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Development of the quinolones

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Since their discovery in the early 1960s, the quinolone group of antibacterials has generated considerable clinical and scientific interest. Nalidixic acid, the first quinolone to be developed, was obtained as an impurity during the manufacture of quinine. Since this time, many derivatives have been synthesized and evaluated for their antibacterial potency. Two major groups of compounds have been developed from the basic molecule: quinolones and naphthyridones. Manipulations of the basic molecule, including replacing hydrogen with fluorine at position 6, substituting a diamine residue at position 7 and adding new residues at position 1 of the quinolone ring, have led to enhanced antibacterial efficacy. In general these compounds are well tolerated. However, some of these structural changes have been found to correlate with specific adverse events: the addition of fluorine or chlorine at position 8 being associated with photoreactivity, e.g. Bay y 3118 and sparfloxacin; and the substitution of an amine or a methyl group at position 5 having a potential role in QTc prolongation, e.g. sparfloxacin and grepafloxacin. Progressive modifications in molecular configuration have resulted in improved breadth and potency of *in vitro* activity and pharmacokinetics. One of the most significant developments has been the improved anti-Gram-positive activity of the newer compounds, such as moxifloxacin and garenoxacin. In the current millennium, these new agents may play an important role in the treatment of respiratory infections.

Keywords: quinolones, pharmacokinetics, pharmacodynamics, drug development

Introduction

Quinolones have been the centre of considerable scientific and clinical interest since their discovery in the early 1960s. This is because they potentially offer many of the attributes of an ideal antibiotic, combining high potency, a broad spectrum of activity, good bioavailability, oral and intravenous formulations, high serum levels, a large volume of distribution indicating concentration in tissues and a potentially low incidence of side-effects. Much research has attempted to make these potential attributes real. Nalidixic acid was the first quinolone to be developed (Table 1), but it took more than a decade before additional compounds, such as flumequin, norfloxacin and enoxacin became available for clinical use. The main use for all these agents was the treatment of urinary tract infection. In the late 1980s more systemically active drugs, such as ciprofloxacin and ofloxacin, were marketed. Recently, there has been a considerable increase in the number of agents that are in development, and to date over 10 000 molecules have been patented. This review will trace the development of quinolones from their sole use as treatment for urinary tract infections, via systemic use, to those agents whose primary use is for the treatment of respiratory tract infections. This development may be described in terms of structures, potency, pharmacokinetics and pharmacodynamics, and finally indications and clinical use.

Structural developments

Quinolones were derived from quinine. Figure 1 shows the basic fluoroquinolone molecule or 'pharmacore'.[1] The addition of a fluorine molecule at position 6 was one of the earliest changes to the structure. This single alteration provides a more than 10-fold increase in gyrase inhibition and up to 100-fold improvement in MIC. Two major groups have been developed from the basic structure: quinolones and naphthyridones.[1–5] The presence of a nitrogen at position 8 identi-

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Table 1. Chronology of quinolones that reached the UK market

Date	Quinolone
1960–1969	nalidixic acid
1970–1975	cinoxacin
1975–1985	norfloxacin
1985–1990	ciprofloxacin, ofloxacin
1990–1995	temafloxacin, sparfloxacin
1995–2000	grepafloxacin, levofloxacin, trovafloxacin
2000–2005	moxifloxacin, possibly gemifloxacin and garenoxacin in 2003 or later

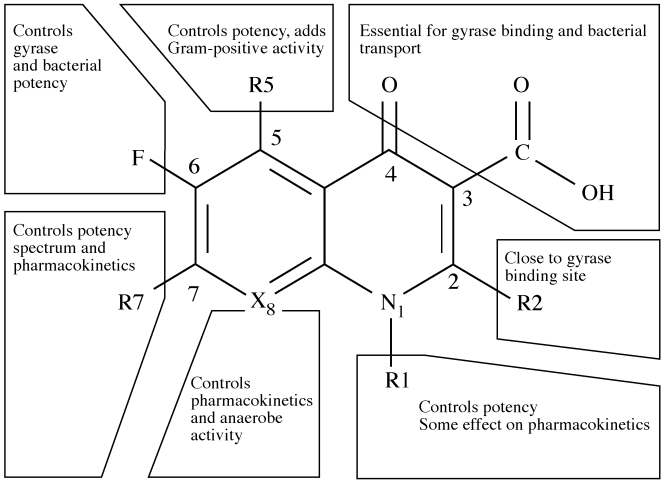

Figure 1. Structure of the quinolone and napthyridone molecule. In molecules where X is a carbon atom, the molecule is a quinolone (cinoxacin, norfloxacin, ofloxacin, ciprofloxacin, temafloxacin, sparfloxacin, grepafloxacin, levofloxacin, clinafloxacin, moxifloxacin, gatifloxacin). Where X is a nitrogen atom the molecule is a naphthyridone (nalidixic acid, enoxacin, tosufloxacin, trovafloxacin, gemifloxacin). Adapted from Domagala (1994).[2]

fies the naphthyridones, a carbon and associated group at position 8 identifies the quinolones.[1–5]

The quinolones and napthyridones were further enhanced by the addition of groups to the N_1, C-5 and C-7 positions of their respective basic molecules. The addition of piperazine to the C-7 position (e.g. norfloxacin) improves activity against Gram-negative organisms. There are data to suggest that a piperazine ring may play a role in inhibiting efflux mechanisms, thereby improving the potency of these drugs. The structure of norfloxacin illustrates these developments and subsequent to this all quinolones (except garenoxacin) have a fluorine at position 6 and many have six-membered rings at position C-7 (Figure 2). The presence of a pyrrolodinyl group at position C-7 (e.g. clinafloxacin) improves activity against

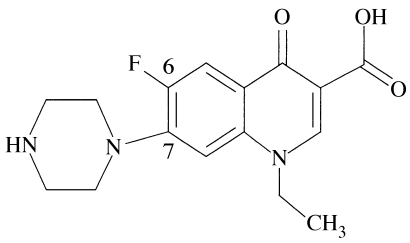

Figure 2. Modifications of quinolone structures: norfloxacin. In all subsequent molecules, except garenoxacin, fluorine was retained at position 6. A six-membered ring at position 7 is found in ciprofloxacin, temafloxacin, sparfloxacin, ofloxacin and levofloxacin.

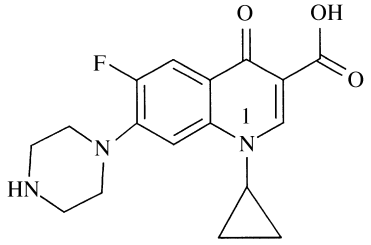

Figure 3. Modification of quinolone structures: ciprofloxacin. A cyclopropyl group at position 1 is found in sparfloxacin, grepafloxacin, clinafloxacin, gatifloxacin, moxifloxacin and garenoxacin.

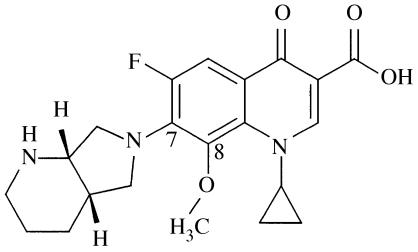

Figure 4. Modification of quinolone structures: moxifloxacin. A five-membered ring or azabiocyclo rings at position 7 are found in clinafloxacin and trovafloxacin (five-membered ring) or moxifloxacin and garenoxacin (azabicyclo rings). A methoxy group at position 8 is found in moxifloxacin and gatifloxacin. A difluoromethyl ether (OHF_2) group is found at position 8 in garenoxacin.

Gram-positive organisms. In addition to piperazine at the C-7 position, a cyclopropyl group was introduced to the N_1 position and is best exemplified by ciprofloxacin, which was first synthesized in 1983 (Figure 3). This increases the potency of the drug and many subsequent quinolones have a cyclopropyl group (e.g. grepafloxacin, moxifloxacin, gatifloxacin and garenoxacin; Figure 4). The addition of a 2,4-difluorophenyl group at position 1 (e.g. trovafloxacin) also improves potency, especially in improving activity against anaerobes.

A number of other structural manipulations have been tried to improve the anti-Gram-positive activity of fluoroquinolones. One of the first additions was an NH_2 group at position

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C-5, which resulted in a general increase in anti-Gram-positive activity. This is seen with sparfloxacin which otherwise has a very similar structure to ciprofloxacin. Sparfloxacin also has a fluorine at position C-6, a piperazine at position C-7 and is alkylated. Grepafloxacin is also substituted at position C-5 but by a CH_3 group and has improved anti-Gram-positive potency compared with ciprofloxacin. The substituents at position C-7 are associated with a number of key attributes, such as antibacterial spectrum, bioavailability and side-effects. The most common substituents are cyclic amino groups, for example piperazine or pyrrolidine rings; other groups have been less successful. Piperazine rings are particularly common (e.g. norfloxacin, enoxacin or ciprofloxacin) and confer potency against Gram-negative bacteria. The addition of methyl groups can improve both oral absorption and *in vivo* activity. However, the improved activity against Gram-positive bacteria can sometimes be at the expense of activity against *Pseudomonas aeruginosa*.

Pyrrolidine rings (five-membered) are also common substituents at position 7, and are associated with enhanced potency against Gram-positive bacteria. However, this group is associated with low water solubility and low oral bioavailability so *in vivo* activity may be compromised. Introduction of methyl groups on the pyrrolidine ring helps to overcome some of these physical properties. Gemifloxacin, a naphthyridone, is a good example of the advantages and disadvantages associated with a pyrrolidine ring at position 7.[6] The addition of azabicyclo groups onto position 7 has resulted in agents (moxifloxacin and trovafloxacin) with significant anti-Gram-positive activity, marked lipophilicity and half-lives of >10 h.[7,8]

Manipulation of the group at position 8 has also been shown to play a role in altering oral pharmacokinetics, broadening the spectrum of activity and reducing the selection of mutants.[9–13] Whilst alkylation has been shown to increase further anti-Gram-positive activity, it also improves tissue penetration and extends the half-life by increasing lipophilicity, as with grepafloxacin, levofloxacin and sparfloxacin.

The structural changes to the quinolone molecule and correlation with adverse events are now well documented.[3,14] Photo-reactivity is probably most influenced by position 8, with fluorine or chlorine producing most phototoxic potential (e.g. lomefloxacin, clinafloxacin, Bay y 3118 and sparfloxacin) and methoxy groups the least (e.g. moxifloxacin or gatifloxacin). Garenoxacin has fluorine incorporated through a C-8 difluoromethyl ether linkage as there is no fluorine at C-6. It has been suggested that substitution at position 5 may have a role in QTc prolongation as those agents that have been associated with significant problems, such as sparfloxacin and grepafloxacin, have either a NH_2 or a CH_3 group in this position.[15,16]

Much speculation has also surrounded the likely structural correlates of the haemolytic uraemic-like syndrome caused by temafloxacin,[17] hepatic eosinophilia caused by trovafloxacin,[18] pulmonary interstitial eosinophilia and other immunological side-effects caused by tosufloxacin[19] and gemifloxacin, and the hypoglycaemia seen with temafloxacin and clinafloxacin.[18,20,21] Although a number of these agents are naphthyridones (trovafloxacin, tosufloxacin and gemifloxacin) others are fluoroquinolones (temafloxacin), hence it is unclear whether this difference is relevant. A more powerful association is that of the 2,4-difluorophenyl group at position 1, as this is shared by trovafloxacin, temafloxacin and tosufloxacin[1] but not by gemifloxacin.[6] A further hypothesis is that metabolites of these agents (as yet not fully identified), which share common structures, may be responsible for some of the immunologically mediated adverse events seen with these drugs.

The naphthyridones can be modified by the addition of cyclopropyl groups in the same way as the quinolones. A five-membered ring has been added to the molecule of gemifloxacin at position 7. Trovafloxacin has an azabicyclo ring, which improves anti-Gram-positive activity, increases the half-life and results in resistance to efflux pumps.[8]

Developments in potency

The development of these agents can be described in terms of their potency against Gram-positive, Gram-negative or atypical bacteria. In terms of anti-Gram-negative potency, as indicated by MIC_{90}s, the activity of quinolones against Enterobacteriaceae such as *Escherichia coli* and *Klebsiella* spp. has not changed significantly since the development of norfloxacin (Table 2).[6,22–31] In terms of their MIC_{90}s, the early drugs (nalidixic acid and cinoxacin) did not have very good anti-pseudomonal potency. In general, the newer agents have improved activity against pathogens such as *Mycoplasma pneumoniae* and other atypical bacteria, and some have improved activity against Gram-negative anaerobes, such as *Bacteroides fragilis* (Tables 2 and 3). However, many of the newer agents, such as gatifloxacin, gemifloxacin, garenoxacin and moxifloxacin, are not as potent as ciprofloxacin against *P. aeruginosa*.

One of the more interesting developments in terms of potency is the area of anti-Gram-positive activity. Although it is unlikely any fluoroquinolone will have activity against ciprofloxacin-resistant *Staphylococcus aureus*, a major development has been in the activity of these drugs against ciprofloxacin-sensitive *S. aureus, Streptococcus pneumoniae* and Group A streptococci.[10,12,32–35] This is one of the key advances in terms of the development of these agents.

Table 4[22–31,36–39] lists the fluoroquinolones on the basis of their MIC_{90}s for five Gram-positive species. Nalidixic acid, cinoxacin and enoxacin have no activity at all, whereas gemifloxacin has an MIC_{90} of 0.03 mg/L for *S. pneumoniae*, and is

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Table 2. Development of quinolone potency against Gram-negative bacteria

	MIC_{90} (mg/L)						
Quinolone	*E. coli*	*Klebsiella* spp.	*Enterobacter/ Citrobacter* spp.	*Serratia* spp.	*Haemophilus influenzae*	*P. aeruginosa*	*B. fragilis*
Nalidixic acid	8	16	>64	>64	2	>64	>64
Cinoxacin	8	8	>64	>64	2	>64	>64
Enoxacin	0.25	2	1	4	0.12	2	>64
Norfloxacin	0.12	0.5	0.25	2	0.06	2	>64
Ciprofloxacin	0.03	0.25	0.12	0.5	0.03	1	16
Ofloxacin	0.12	0.5	0.5	1	0.03	4	16
Levofloxacin	0.12	0.25	0.5	0.5	0.03	2	8
Temafloxacin	0.06	0.5	0.5	0.5	0.03	1	4
Trovafloxacin	0.06	0.25	0.06	1	0.01	1	0.25
Clinafloxacin	0.01	0.03	0.12	0.25	0.01	0.5	0.25
Sparfloxacin	0.06	0.5	0.5	4	0.03	4	4
Grepafloxacin	0.06	0.12	0.5	2	0.01	8	8
Moxifloxacin	0.06	0.12	1	2	0.06	8	1
Gatifloxacin	0.06	0.25	0.5	1	0.03	4	1
Gemifloxacin	0.03	0.25	0.5	2	0.06	4	ND
Garenoxacin	0.06	0.5	1.0	2	0.03	16	1

Table 3. Development of quinolone potency against atypical bacteria

	MIC_{90} (mg/L)				
Quinolone	*Legionella pneumophila*	*M. pneumoniae*	*Chlamydia* spp.	*Mycoplasma hominis*	*Ureaplasma urealyticum*
Nalidixic acid	0.25	>64	>64	>64	>64
Enoxacin	0.12	4	8	8	16
Norfloxacin	0.06	16	16	8	16
Ciprofloxacin	0.01	2	2	1	4
Ofloxacin	0.03	2	2	0.5	1
Levofloxacin	0.01	1	1	0.25	1
Trovafloxacin	0.01	0.25	0.12	0.5	0.5
Clinafloxacin	0.008	0.03	0.12	0.03	0.12
Sparfloxacin	0.06	0.5	0.5	0.5	0.5
Grepafloxacin	0.01	0.5	0.12	0.12	0.5
Moxifloxacin	0.01	0.12	0.12	0.06	0.25
Gatifloxacin	0.01	0.12	0.25	0.12	0.25
Gemifloxacin	0.008	0.12	0.06	0.01	0.25
Garenoxacin	0.008	0.06	0.016	0.03	0.06

equivalent to the earlier compounds in terms of activity against the majority of Gram-negatives (Table 2). The activity against enterococci is less clearly defined because different species are often classified together, and the proportions of *Enterococcus faecium* and *Enterococcus faecalis* are not provided. This is important as *E. faecium* is more resistant than *E. faecalis*.

Developments in pharmacodynamics and pharmacokinetics

Pharmacokinetics (PK) refers to changes in drug concentration as the drug moves through the body, whilst pharmacodynamics (PD) refers to how the drug action changes with concentration or dose.

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Table 4. Development of quinolone potency against Gram-positive bacteria

	MIC_{90} (mg/L)				
Quinolone	*S. aureus* (methicillin sensitive)	*S. pneumoniae*	Group A streptococci	*Enterococcus* spp.	*Clostridium perfringens*
Nalidixic acid	>64	>64	>64	>64	>64
Cinoxacin	>64	>64	>64	>64	>64
Enoxacin	2	64	64	8	>64
Ciprofloxacin	1	2	1	4	0.5
Ofloxacin	0.5	2	2	2	1
Levofloxacin	0.25	1	1	2	0.5
Temafloxacin	0.25	0.5	0.5	2	1
Sparfloxacin	0.12	0.5	1.0	2	0.25
Grepafloxacin	0.12	0.25	1.0	4	1
Gatifloxacin	0.25	0.25	0.25	1	0.5
Trovafloxacin	0.03	0.12	0.25	1	0.25
Moxifloxacin	0.06	0.12	0.25	2	0.25
Clinafloxacin	0.06	0.12	0.06	0.25	0.12
Gemifloxacin	0.06	0.03	0.06	4	ND
Garenoxacin	0.03	0.12	0.25	0.5	0.25

Table 5. Development of quinolone pharmacokinetics

Quinolone	Dose (g) (frequency per day)	C_{max} (mg/L)	AUC (mg·h/L)	Half-life (h)	Protein binding (%)	Elimination route
Nalidixic acid	1 (×4)	variable	variable	1.5	90	renal
Enoxacin	0.5 (×2)	1.5	19	2	60	renal
Enoxacin	0.6 (×1)	3.7	29	6	70	renal
Norfloxacin	0.4 (×2)	1.5	10	3	15	renal and hepatic
Ciprofloxacin	0.75 (×2)	3.5	30	4	40	renal and enteral
Ofloxacin	0.4 (×2)	4.8	64	6	40	renal
Levofloxacin	0.5 (×1)	5.2	48	7	40	renal
Temafloxacin	0.6 (×2)	7.0	134	8	25	renal
Trovafloxacin	0.3 (×1)	2.5	40	12	85	hepatic
Clinafloxacin	0.2 (×2)	1.6	18	6	40	renal
Sparfloxacin	0.4 (×1)	1.0	20	18	40	renal and hepatic
Grepafloxacin	0.4 (×1)	1.4	14	14	50	hepatic
Moxifloxacin	0.4 (×1)	3.1	30	13	50	hepatic
Gatifloxacin	0.4 (×1)	4.0	37	9	20	renal
Gemifloxacin	0.32 (×1)	1.0	9	7	60	renal and other
Garenoxacin	0.4 (×1)	5.8	59	15	87	renal and other

Nalidixic acid is a drug that is excreted in urine and has very variable systemic absorption. Essentially it is not a systemic drug, but a urinary agent. Over time, larger serum area under the curve (AUC) or peak serum (C_{max}) values are consistently seen as the quinolones have developed, and oral absorption has markedly improved compared with that of nalidixic acid (Table 5).[6,30,31,40,41] The half-life of these agents has also tended to increase as structural modifications have been made to the molecule. However, since the activity of quinolones is concentration dependent, meaning that the extent of bacterial killing increases as drug concentrations increase, and they have a prolonged post-antibiotic effect (PAE),[42] a long half-life is not an absolute prerequisite for once-daily dosing.[14,43,44] No trend in protein binding has become apparent over time with some agents having a binding of <30% (norfloxacin, temafloxacin and gatifloxacin) and others >70% (nalidixic

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Table 6. Development of quinolone pharmacodynamics against Gram-negative pathogens

AUC/MIC (total)	*E. coli*	*H. influenzae*	*P. aeruginosa*
<12.5	nalidixic acid	nalidixic acid	nalidixic acid, enoxacin, norfloxacin, sparfloxacin, grepafloxacin, moxifloxacin, gatifloxacin, gemifloxacin, garenoxacin
12.5–25			enoxacin, ofloxacin
25–50			ciprofloxacin, levofloxacin, trovafloxacin, clinafloxacin
50–100	norfloxacin		
>100	all others	all others	temafloxacin

Table 7. Development of quinolone pharmacodynamics against Gram-positive pathogens

AUC/MIC (total)	*S. aureus*	*S. pneumoniae*	Group A streptococci
<12.5	nalidixic acid, cinoxacin, norfloxacin	nalidixic acid, cinoxacin, enoxacin, norfloxacin	nalidixic acid, cinoxacin, enoxacin, norfloxacin
12.5–25	enoxacin	ciprofloxacin	sparfloxacin, grepafloxacin
25–50	ciprofloxacin	ofloxacin, levofloxacin, grepafloxacin	ciprofloxacin, ofloxacin, levofloxacin
50–100		sparfloxacin	
>100	ofloxacin, levofloxacin, temafloxacin, trovafloxacin, clinafloxacin, grepafloxacin, moxifloxacin, gatifloxacin, gemifloxacin, garenoxacin	temafloxacin, trovafloxacin, clinafloxacin, moxifloxacin, gatifloxacin, gemifloxacin, garenoxacin	temafloxacin, trovafloxacin, clinafloxacin, moxifloxacin, gatifloxacin, gemifloxacin, garenoxacin

acid, enoxacin, trovafloxacin and garenoxacin). Non-renal clearance seems to have become a feature of a number of the newer agents (e.g. trovafloxacin, grepafloxacin, moxifloxacin and garenoxacin), although many fluoroquinolones and naphthyridones are eliminated primarily by metabolism and renal clearance (glomerular filtration and active tubular secretion). Clearly, a high free-drug C_{max} and AUCs, combined with lower MIC, are a significant advance because they will have the effect of increasing the value of C_{max}/MIC or AUC/MIC ratios.

There is always a certain amount of debate as to whether the C_{max}/MIC or the AUC/MIC is more important in terms of fluoroquinolone bacteriological and clinical outcomes in man. This is probably not important because the co-variable nature of these two pharmacokinetic parameters makes it difficult to identify which one is dominant in determining microbiological and clinical outcome. In general, agents with large AUC also have high C_{max} concentrations. The other area of considerable pharmacodynamic debate has been what breakpoint or critical PK/PD ratio is required to optimize microbiological or clinical outcomes. For example, if there is a range of values, the bigger numbers are more likely to be predictive of good clinical outcome in terms of the microbiology and the emergence of resistance.[45] At present it is reasonable to assume that almost all the drugs that have AUC/MIC ratios >100 are likely to have useful activity against Enterobacteriaceae and *P. aeruginosa*, while a target of free AUC/MIC of 30–40 is required for *S. pneumoniae*.[46]

For predicting efficacy against most infections, pharmacodynamic variables (for example, AUC/MIC or C_{max}/MIC) are driven by changes in potency, much more than they are driven by changes in pharmacokinetics. The MIC changes are sometimes 100-fold between agents, whereas the pharmacokinetic changes are probably at most five-fold between any of these agents. For example, as ciprofloxacin has an AUC/MIC between 25 and 50 for the therapy of *P. aeruginosa*, it can be anticipated that levofloxacin, trovafloxacin and clinafloxacin will have similar activity to ciprofloxacin against *P. aeruginosa* (Table 6).[47,48] In contrast, some of the newer drugs, such as grepafloxacin, moxifloxacin, gatifloxacin, sparfloxacin, gemifloxacin or garenoxacin, together with some of the older urinary drugs like norfloxacin, are unlikely to have significant clinical activity against *P. aeruginosa* at present doses. Pharmacodynamics would predict that all but the very early quinolones will have good clinical activity

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Table 8. Proposed classification of fluoroquinolones

Agents	Activity	Clinical applications
Urinary agents (1960–1985)		
nalidixic acid cinoxacin enoxacin norfloxacin	activity against common Enterobacteriaceae, short serum half-lives, renal elimination	main use in UTI
Gram-negative systemic agents (1985–1995)		
ciprofloxacin ofloxacin levofloxacin	wide activity against Gram-negatives, including *P. aeruginosa*, marginal activity against Gram-positives, longer serum half-lives	widely used against tissue-based and urinary infections
Broad spectrum systemic agents (1990–2000)		
temafloxacin clinafloxacin trovafloxacin	wide activity against Gram-negatives, including *P. aeruginosa* for some agents, and Gram-positives, for some agents long serum half-lives, some activity against anaerobes	widely used against a broad range of tissue-based infections
Respiratory agents (1995 onwards)		
levofloxacin sparfloxacin grepafloxacin moxifloxacin gatifloxacin gemifloxacin garenoxacin	wide activity against Enterobacteriaceae, active against Gram-positives, especially *S. pneumoniae*, active against atypical bacteria, variable activity against anaerobes, long serum half-life	main use in respiratory tract infection

against *E. coli* and *H. influenzae* causing systemic infection (Table 6).

With respect to the Gram-positive organisms, it is clear that the urinary drugs are not going to have useful clinical activity against *S. pneumoniae*, *S. aureus* or *Streptococcus pyogenes* (Table 7). Whereas with ofloxacin, levofloxacin, grepafloxacin and sparfloxacin, AUC/MIC ratios of >25 are beginning to predict clinically useful outcomes for non-immunocompromised patients with mild to moderate community-acquired disease. In the context of immunocompromised patients (those with co-morbidity or ITU patients) or in order to prevent the emergence of resistance, ratios should probably be higher. The more recently developed fluoroquinolones, such as trovafloxacin, gatifloxacin, gemifloxacin, moxifloxacin and garenoxacin, are likely to have useful clinical activity against *S. pneumoniae*, a prediction now supported by clinical trials data in community-acquired pneumonia[49] and acute exacerbation of chronic bronchitis (AECB).[50,51] The small amount of existing clinical data also implies that these agents are clinically active against ciprofloxacin-susceptible *S. aureus* and Group A streptococci.[32–35,52]

Toxicology

Many of the more recently developed quinolones do not have the toxicological disadvantages of the earlier compounds, for example the QTc prolongation that has limited the use of sparfloxacin and grepafloxacin. Other effects include a haemolytic uraemic-like syndrome with temafloxacin,[17] a metallic taste with grepafloxacin,[53] hepatitis with trovafloxacin,[54] unexpected hypoglycaemia with clinafloxacin and temafloxacin,[21,55,56] a number of immunologically mediated adverse events with tosufloxacin,[18] and an immune-mediated rash in young women with gemifloxacin.[6] To date there are little toxicological data on garenoxacin.

Indications and use

The pharmacokinetic and *in vitro* potency profiles of fluoroquinolones determine the areas of clinical use. This has shifted from agents used predominantly for the treatment of urinary tract infections in the 1960s/70s, to more systemic use in the 1980s/90s, and in the current millennium, to the treatment of respiratory tract infections. Sparfloxacin and grepa-

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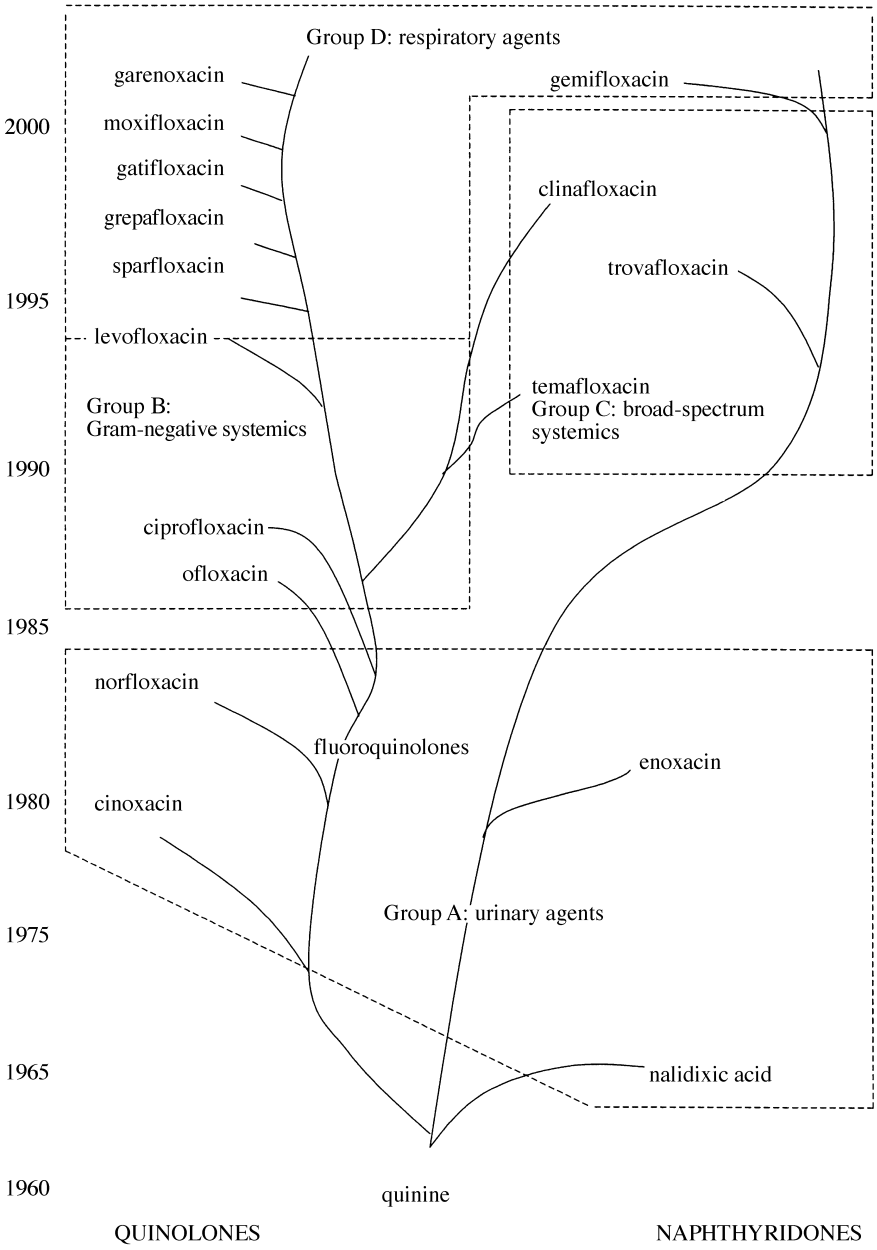

Figure 5. Development of quinolones.

floxacin were the first agents to focus on the respiratory tract, exploiting their activity against *S. pneumoniae* and atypical organisms. More recently a further group of agents (moxifloxacin, gatifloxacin, gemifloxacin and garenoxacin) with more convincing potential in the respiratory tract have been developed. Thus development has moved from the urinary to the respiratory tract via a miscellaneous group of systemic indications. Levofloxacin is one example of a drug where there is a wide range of potential uses, but in terms of marketing the main focus appears to be respiratory.

On this basis, quinolones can be classified into four groups according to clinical use, potency, pharmacokinetics and pharmacodynamics. The first group consists of urinary agents that are, in general, the older drugs which are active against the common Enterobacteriaceae and tend to have short half-lives and renal elimination (Table 8). The second group includes the anti-Gram-negative systemic agents such as ciprofloxacin, levofloxacin and ofloxacin which, according to their pharmacokinetics and activity, indicate that they can be used for Gram-negative infection and as anti-pseudomonal agents. There is, however, debate about their use in various areas of Gram-positive infection. The third group, of which trovafloxacin and temafloxacin are the best examples, have sufficiently broad activity in terms of anti-Gram-negative,

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anti-Gram-positive, antipseudomonal and anti-anaerobic activity, to indicate their use for a wide range of tissue-based infections. The fourth group includes the respiratory agents, some of which are also in other categories. These drugs have activity against *S. pneumoniae* and atypical organisms, but are less active against *P. aeruginosa.* Some of these agents, such as moxifloxacin and garenoxacin, may be as active as trovafloxacin against anaerobes, suggesting that with time, their clinical indications may expand beyond the respiratory area. The nomenclature of the quinolones is complex, and these agents have also been classified in terms of generation[57] (discussed in this supplement in the article by P. Ball). However, whichever classification is used, it is clear that these agents are not a homogeneous group of antibiotics, and that important differences exist between them.

Conclusions

Modifications in the basic structure of quinolones have increased their antibacterial spectrum and potency, as well as improving bioavailability, making quinolones useful agents for the treatment of urinary, systemic and respiratory tract infections. An 'evolutionary' tree is shown in Figure 5. However, safety concerns continue with some members of this class and have resulted in the withdrawal of some agents after marketing (temafloxacin, grepafloxacin, sparfloxacin, trovafloxacin) or others in late development (clinafloxacin and gemifloxacin). It is still unclear as to which structure–function relationships have resulted in these problems, so despite a good deal of progress being made in terms of *in vitro* activity and pharmacodynamics, progress in the area of toxicology has been erratic.

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