REVIEW ARTICLE

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Comparative Tolerability of the Newer Fluoroquinolone Antibacterials

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Abstract

The most common adverse effects of the fluoroquinolones involve the gastrointestinal tract, skin and CNS, and are mainly mild and reversible. Of the gastrointestinal events, nausea and vomiting are the most common.

Mild hepatic reactions are a class effect, usually presenting as mild transaminase level increases without clinical symptoms. However, postmarketing surveillance has revealed significant hepatotoxicity with trovafloxacin. It is not currently known whether the severe reactions to trovafloxacin are specific to that agent or simply represent an extreme of an emerging class effect. The enormous worldwide usage of, and extensive published adverse effect data on the other fluoroquinolones and naphthyridones suggests the former. In perspective, rare but serious hepatotoxicity has been reported with other fluoroquinolones and the overall incidence of trovafloxacin hepatotoxicity is not dissimilar to that reported with flucloxacillin and amoxicillin-clavulanic acid.

CNS reactions vary in severity and include dizziness, convulsions (notably with lomefloxacin) and psychoses. Fluoroquinolones differ in their pro-convulsive activity, relating to their differing potential as γ-aminobutyric acid antagonists and binding to the *N*-methyl-D-aspartate receptor. The basis for the increased seizure potential following the coadministration of nonsteroidal anti-inflammatory drugs with certain fluoroquinolones is not fully understood.

Fluoroquinolone phototoxicity, caused by the generation of toxic free oxygen species under exposure to UVA radiation, is significantly more common with 8-halogenated compounds. Certain patient groups, e.g. patients with cystic fibrosis, are predisposed to this adverse effect. Murine photocarcinogenicity has been demonstrated with lomefloxacin, but no such effects have been reported in humans.

Prolongation of the QTc interval is also a class effect, although cardiac arrhythmias have only been linked with sparfloxacin. Among the newer fluoroquinolones, clinically significant cardiac events are rare or absent but possible interactions in patients receiving other drugs capable of causing QT prolongation should be anticipated.

Tendinitis and rupture, usually of the Achilles tendon, are rare, class-effects of fluoroquinolones, most frequently reported with pefloxacin. Predisposing factors include aging, corticosteroid use, renal disease, haemodialysis and transplantation.

Use of fluoroquinolones in paediatric patients remains contentious. However, accruing human data suggest that restrictions on paediatric use imposed because of fluoroquinolone-induced cartilage damage in juvenile animals, may soon be relaxed. Data from over 1700 children in the UK failed to disclose arthropathy and extensive paediatric use of norfloxacin in Japan and ciprofloxacin in developing countries has been free of articular effects.

Five years ago, we reviewed the first 10 years' experience of tolerability and adverse drug reactions of a new class of antibacterial: the fluoroquinolones.[1] At that time, the temafloxacin syndrome had led to the withdrawal of that agent.[2] In addition, the investigation of several new compounds, including the promising Bay y 3118 had been discontinued because of phototoxicity, and the investigation of yet others, including sitafloxacin (DU-6859a) and clinafloxacin, had been delayed because of similar adverse effects. Fluoroquinolone development, at least in Western countries, appeared to be at a standstill.[3] Nevertheless, at that time most adverse effects associated with fluoroquinolone therapy were well recognised and there was, perhaps, little left to say in respect of fluoroquinolone development, except in the intriguing debate surrounding paediatric use.[4,5]

However, the last 5 years have seen the development and marketing of a number of new compounds with improved activity, notably against Gram-positive pathogens (particularly pneumococcus), and improved kinetics permitting once daily dosage.[6] These compounds include sparfloxacin, grepafloxacin, and the 7-azabicyclo derivatives trovafloxacin and moxifloxacin. In addition, the *L*-enantiomer of ofloxacin (levofloxacin) became available. These agents are now available in many countries and the more active compounds, notably the more active 7-azabicyclo derivatives, have excellent *in vitro* and clinical activity.[3,6]

Therefore, unless and until statistically and clinically significant differences in clinical efficacy between these new fluoroquinolones have been reported in either post-registration trials or pharmacoeconomic analyses, the only clear discriminants

between compounds are likely to be acquisition cost and adverse effect profiles. The former are outside the scope of this article: the latter may justify it. Further justification is provided by the many other compounds in development, such as gatifloxacin, the new fluoroquinolones that are currently in development in Japan, the 7-chloro compounds (clinafloxacin and sitafloxacin), and gemifloxacin (SB 265805).

Thus, 5 years on from our original review, it is necessary to consider the evidence accumulating on both existing and new fluoroquinolones, such that rational judgements regarding their use may be made on grounds of both clinical utility and safety.[1] Our previous article has provided a basis for this review, but the data reviewed in it are not reiterated.

1. Data Sources

The data referred to in this article have been obtained from our previous article,[1] published papers in peer-reviewed journals and supplements, company sponsored publications, and data from articles in press or which have been, or are to be presented at international congresses. Company data on file have been used only where no other source is available. Data have also been obtained from registration/licensing authorities, including the US Food and Drug Administration (FDA)[7,8] [under the provisions of the US freedom of information legislation] and European Agency for the Evaluation of Medicinal Products (EMEA). Documents from these registration and licensing authorities regarding trovafloxacin hepatic reactions, including press releases, talk papers and interim recommendations are identified separately.

2. Previous Reviews of Fluoroquinolone Adverse Effect Data

To date, after almost 15 years of general clinical use, major or life-threatening adverse effects related to fluoroquinolone use have been extremely uncommon. Up until recently the most notable exception to this was the temafloxacin syndrome, which consisted of serious haemolysis, organ dysfunction and, in some cases, death. The mechanism behind this syndrome still remains unexplained.[2] The tolerability of the second generation fluoroquinolones (see table I for classification) has been exhaustively reviewed elsewhere.[1,9-15]

It is recognised that certain nuclear and side-chain configurations are associated with altered frequencies of particular adverse effects.[16] These include the following:

- unsubstituted 7-piperazine: high epileptogenicity, interaction with nonsteroidal anti-inflammatory drugs (NSAIDs)
- 7-aminopyrrolidine: low epileptogenicity, minor interaction with NSAIDs
- bulky 7-substitutions: low γ-aminobutyric acid (GABA) receptor binding
- 8-haloquinolones (Cl, F): phototoxicity (notably 7-chloro derivatives, e.g. clinafloxacin, sitafloxacin, Bay y 3118)
- 1-difluorophenyl: relationship to temafloxacin syndrome?
- naphthyridone nucleus: potentially increased adverse effects overall, e.g. enoxacin, tosufloxacin, trovafloxacin.

Fluoroquinolone adverse effects mostly affect the gastrointestinal system, skin and CNS, are usually mild and reversible and rarely require treat-

Table I. Classification of the second and third generation of fluoroquinolones[3]

Second generation
Group IIA[a]
Ciprofloxacin, ofloxacin, levofloxacin, pefloxacin, norfloxacin, lomefloxacin, fleroxacin
Group IIB[b]
Sparfloxacin, tosufloxacin, grepafloxacin, temafloxacin
Third generation[c]
7-azabicyclo compounds:
Trovafloxacin[d], moxifloxacin (8-methoxyquinolone)[e]
Agents in development:
Clinafloxacin, sitafloxacin (8 fluoro compounds), gatifloxacin (8-methoxyquinolone), gemifloxacin, balofloxacin

a Predominantly Gram-negative activity.
b Balanced broad-spectrum activity.
c Markedly increased anti–Gram-positive potency.
d Restricted or license suspended.
e Licensed in Germany, US decision pending.

ment intervention.[1] The adverse effect rates for second generation fluoroquinolones were covered in our previous review[1] and these data, together with those for later second and new third generation compounds (see table I for classification), are now summarised in table II. Data specifically relating to Japanese patients, in whom lower rates of adverse effects with fluoroquinolones usually apply and in whom fluoroquinolones that have not used in Western countries have been studied, are detailed in table III.

Subsequent to our original review,[1] prescription event monitoring studies of ciprofloxacin, norfloxacin and ofloxacin in large patient cohorts have reported no new adverse effects.[29] Event rates within the basic gastrointestinal, CNS and dermatological categories have remained consistent. New data presented on the use of fluoroquinolones during the first trimester of pregnancy have revealed neither congenital abnormalities nor fluoroquinolone-associated deaths.[29]

Initial analysis of fluoroquinolone adverse effects suggested that most occurred with the first 7 to 10 days of therapy.[30] The prescription event monitoring study of ciprofloxacin, norfloxacin and ofloxacin confirms this view.[29] A review of ciprofloxacin data available up to 1997 paints a similar picture, with most adverse effects occurring early during therapy with little increment over time.[31] The overall incidence of adverse effects was 23% for the ciprofloxacin group and 25% in control participants. Half of all events occurred within 10 days of starting treatment; 90% occurred within 30 days. The incidences of adverse effects per 100 treatment days were: 1.1 for ciprofloxacin, 1.5 for the control group and, 3.5 for combinations of ciprofloxacin plus at least 1 other antibacterial.

3. Drug-Related Discontinuation Rates

Numerous factors confound comparisons between overall and treatment-related adverse effect rates obtained from preregistration studies of fluoroquinolones. Discontinuation rates may be a more appropriate measure of true tolerability, although the vagaries of patient choice can rarely be differentiated from discontinuation on clinical grounds by physicians. The following data on discontinuation rates have been obtained from reviews or the FDA-approved datasheet (for levofloxacin):

- levofloxacin (500mg oral): 3.7% overall[32]

Table II. Overall incidence of adverse effects associated with fluoroquinolones (US/European data)

Fluoroquinolone	Total adverse effects (%)	Gastrointestinal effects (%)	CNS effects (%)	Skin effects (%)	Reference
Ciprofloxacin PO	5.8	3.4	1.1	0.7	1
Norfloxacin	9.1	3.9	4.4	0.5	18
Pefloxacin	8.0	5.6	0.9	2.2	19
Ofloxacin	4.2	2.6	0.89	0.53	20
Levofloxacin	2-9.9 (3.3[17])	5.1	0.2-1.1	0.2[17]	15
Lomefloxacin	NS	5.1	5.5	2.4	21
Fleroxacin (400mg/200mg)	21	11.0	9.0	3.0	22
Sparfloxacin (400mg/200mg)	Overall: 32 Related: 25.3[15]	10	>3	1.9 (phototoxicity 7.4[15])	23
Sparfloxacin RTI (400mg/200mg)	Total: 40.9 Related: 13.7	11.4	4.2	5.1	24
Grepafloxacin (600mg)	Related: 47.0	15	5	2.0	25
Trovafloxacin RTI (100mg/200mg)	Related: 12.7	6.1	4.4	0.2	26
Trovafloxacin (100mg/200mg)	27	4-7		1.0	3
Moxifloxacin (400mg)	Related: 27 (comparators 24.5)	8	5.4	2.0	27

PO = oral; **RTI** = respiratory tract infection; **NS** = not stated.

Table III. Overall incidence[a] of drug-related adverse effects associated with fluoroquinolones (Japanese data)[b]

Fluoroquinolone	Total adverse effects (%)	Gastrointestinal effects (%)	CNS effects (%)	Skin effects (%)
Pazufloxacin	3.3	2.1	0.7	0.4
Grepafloxacin	3.5	1.2	1.1	0.8
Tosufloxacin	3.6	2.3	0.75	0.4
Levofloxacin	3.7	2.3	0.55	0.5
Prulifloxacin	3.8	2.25	0.7	0.7
Lomefloxacin	4.3	2.3	1.0	0.4
Gatifloxacin	4.55	2.85	0.55	0.65
Sparfloxacin	5.4	2.35	0.7	0.8
Balofloxacin	5.4	2.6	1.0	0.85
Fleroxacin	5.6	2.4	2.4	0.5
Sitafloxacin[28]	12.5	8.3	1.9	1.15

a Data rounded to nearest 0.05%.

b Data presented at Annual Meetings, Japanese Society of Chemotherapy (Y. Niki, unpublished observations).

- sparfloxacin (400mg/200mg): 3.0 *vs* 2.8% comparators[24]
- grepafloxacin (600mg dose): 6.4 *vs* 1.0% comparators[25]
- trovafloxacin (overall intravenous/oral): 5.7 *vs* 3.3% comparators[33]
- trovafloxacin (prescription-related; patients aged >65 years): 6.6 *vs* 3.3% comparators[34]
- moxifloxacin (400mg dose): 3.3 *vs* 3.2% comparators.[27]

No reference data are currently available for gatifloxacin, gemifloxacin or sitafloxacin.

4. Adverse Effects

4.1 Gastrointestinal Effects

Prescription event monitoring studies show that nausea and vomiting are the most commonly encountered adverse effects (event rates of 3.8 to 4.9 per 1000 patients) associated with second generation fluoroquinolones during therapy.[29] Rates were similar to those for azithromycin and cefixime.[29] Diarrhoea was a significantly lesser problem with fluoroquinolones (event rate 0.9 to 1.8 per 1000 patients) than with cefixime (9.2 per 1000 patients). Pseudomembranous colitis is rare although occasional reports appear.[35,36] None of the older second generation agents can be identified as particularly associated with gastrointestinal adverse effects.

However, taste perversion occurred in up to 26% of patients receiving grepafloxacin 600 mg/day in an early study.[37] This effect was thought to be drug related by 97% of patients. Later trials suggested lower figures of between 4 to 5.5% of patients.[38,39] Analysis of the grepafloxacin pre-registration trials series reveals an overall figure of 17% for treatment-related taste perversion and 15% for nausea, for which 2.6% of all patients discontinued therapy.[25]

In a cohort of 881 patients receiving trovafloxacin for lower respiratory tract infections, nausea, vomiting and diarrhoea were encountered in 2, 1.4 and 1.1% of patients, respectively.[26] However, in the overall pre-registration series, nausea was present in 8% of 3259 patients receiving trovafloxacin 200 mg/day.[33] A similar figure (7.8%) was observed in patients receiving moxifloxacin 400 mg/day, although only 0.85% of patients withdrew from therapy on these grounds, i.e. because of nausea, (data submission to European Registration Authorities, 1998 to 1999.)[40]

4.2 Hepatic Effects

Hepatitis, sometimes severe,[41] hepatic failure (including deaths)[42] and cholestatic syndromes[43,44]

have been observed with second-generation fluoroquinolones.[1] Severe hepatic reactions in experimental animals, including necrosis, have also been observed with some of the newer agents, e.g. trovafloxacin.[45] However, most human hepatic adverse effects are characterised by minor increases (to 3 times the upper limit of normal) in liver transaminase levels, for example in 1 to 2% of patients receiving moxifloxacin and sparfloxacin, respectively.[27,46]

Higher incidences of hepatic enzyme (transaminase) level elevations have been observed with some fluoroquinolones. Abnormal liver biochemistry was noted in 12 to 16% of patients receiving grepafloxacin 300 mg/day during Japanese multicentre studies.[47] Similar increases, sometimes in excess of 3 times the upper limit of normal were noted in 9% of patients receiving trovafloxacin for 28 days.[48] Data from Japan indicate transaminase level elevation in 1.5 to 2.5% of patients taking levofloxacin, prulifoloxacin and temafloxacin, with a slightly higher figure of around 6 to 7.5% for sitafloxacin (Y. Niki, unpublished observation). Significant adverse hepatic effects are in general rare.

However, during postmarketing surveillance of trovafloxacin (a naphthyridone), an apparent excess of spontaneous reports of hepatotoxicity suggested the possibility of an idiosyncratic reaction.[8] Postmarketing surveillance data analysis by Pfizer/Roerig, acting with the FDA[49] and EMEA,[50] in approximately 2.5 million patients treated since February 1998 up to June 1999, identified 140 patients with serious hepatic events including 14 with acute hepatic failure. The majority of patients have recovered completely, but 5 patients required liver transplantation. Five deaths, 1 following liver transplantation, have been associated with trovafloxacin-induced hepatotoxicity although the relationship is not proven. Analysis of the cases has revealed no factors consistently predictive of hepatic toxicity and no subgroup of patients in whom hepatic reactions were more common. No specific structure : hepatotoxicity relationships can be inferred from previous experience with either naphthyridones (enoxacin, tosufloxacin) or di-fluorophenyl substituted fluoroquinolones (temafloxacin).

The hepatic reactions to trovafloxacin occurred between 1 and 60 days after commencement of therapy, were unpredictable and possibly immunoallergic in character. One-third were accompanied by evidence of hypersensitivity reactions and, in a minority of patients, reactions followed exposure to a second course of therapy with either trovafloxacin or another fluoroquinolones. Pancreatitis has also been reported with trovafloxacin, although this does not appear to coexist with hepatic toxicity.[49,50]

Among the first 40 patients to experience a significant hepatic reaction, 6 patients had idiosyncratic eosinophilic hepatitis on liver biopsy (30% of patients experiencing a hepatic reaction had peripheral eosinophilia). Biopsy data from most other fluoroquinolone-associated hepatic reactions are lacking. However, eosinophilic inclusions were noted in norfloxacin-induced centrilobular necrosis[51] and peripheral eosinophilia was present in an elderly woman with norfloxacin-associated cholestasis.[52] Therefore, in addition to transaminase level elevation, eosinophilic hepatitis, perhaps as part of a generalised hypersensitivity reaction, may be an emergent class effect. Other fluoroquinolones will undoubtedly be scrutinised more carefully for potential hepatotoxicity in the future.

For trovafloxacin, licensing authorities have acted quickly, either by restricting usage to (initially) intravenous therapy for life or limb threatening infections in institutionalised patients for whom no other safe and effective therapy is available (USA),[49] or by suspension of the license, initially for a period of 1 year (Europe).[53] In effect, while remaining available for exceptional patients, trovafloxacin has been sequestered from clinical use and, in the light of new fluoroquinolones with at least similar *in vitro* activity, appears unlikely to regain any significant place in therapy.

However, it is important to put trovafloxacin hepatic reactions in context. These events are undoubtedly rare (140 in 2.5 million equates to an incidence of 0.0056%). This is of a similar order to

that of hepatic reactions to flucloxacillin and amoxicillin-clavulanic acid.[54,55] A postmarketing surveillance study of 5 fluoroquinolones immediately subsequent to the withdrawal of temafloxacin found no evidence of significant hepatic reactions.[56] A further postmarketing surveillance study of ciprofloxacin, norfloxacin and ofloxacin, involving in excess of 11 000 patients for each drug, again revealed no attributable cases.[29] Nevertheless, postmarketing surveillance of ciprofloxacin revealed 2 related cases of liver disorder in 37 000 recipients (0.005%)[57] and serious reactions have been reported with ofloxacin, enoxacin, norfloxacin and ciprofloxacin.[41,42,44,51,58]

4.3 CNS Effects

Adverse CNS effects may be trivial, e.g. trovafloxacin- or norfloxacin-induced dizziness, or more severe, e.g. convulsions, which are associated with all of the agents, but particularly with lomefloxacin, or psychiatric reactions, which are possibly more common with ofloxacin.[1]

4.3.1 Minor CNS Effects

The dizziness caused by trovafloxacin therapy is dose-related with an incidence of 11% with a dosage of 200 mg/day.[33] It is usually mild and transient. Commonly a first dose phenomenon, it usually resolves with continued administration.[33] In a cohort of patients treated with trovafloxacin for lower respiratory tract infections, dizziness was reported by only 2% of patients overall and in 1.9% of patients aged less than 65 years.[26] In postmarketing surveillance studies in the US, dizziness was reported in 12.5 per 100 000 patients treated with trovafloxacin, compared with 0.5 per 1 000 000 for levofloxacin.[7,8] This compared with 3 per 100 000 previously reported for norfloxacin in the UK.[1]

With other new agents dizziness is less common, occurring, for example, in 2.9% of patients receiving moxifloxacin.[27] It caused discontinuation of therapy in 0.6% of patients receiving grepafloxacin 600 mg/day,[25] and in 0.5% receiving moxifloxacin 400 mg/day.[25]

4.3.2 Serious CNS Effects

Postmarketing surveillance data on trovafloxacin suggest a higher overall rate of adverse CNS effects than for levofloxacin: 26 per 100 000 patients compared with 4 per 100 000.[7,8] These have included alterations in mentation and affect, confusion and, very rarely, hallucinations and convulsions. All are infrequent and have previously been reported with other fluoroquinolones. Most are trivial, but they may reflect an overall differential interaction with neuro-inhibitory receptors in the brain.

More severe, convulsant effects were reviewed in our previous paper.[1] Studies in cats show differences in the pro-convulsant, excitatory CNS effects of fluoroquinolones, which are thought in part to relate to inhibition of the neuroinhibitory GABA receptor.[59] Effects on GABA receptors probably do explain the interaction between fluoroquinolones and NSAIDs,[60,61] most notably with biphenylacetic acid (BPAA), the active metabolite of fenbufen, which, when coadministered with enoxacin, led to seizures in 7 Japanese patients.[60]

Considerable differences exist between compounds with regard to their activity as GABA antagonists. For example, the inhibitory concentration $(IC)_{50}$ for both ciprofloxacin and sparfloxacin alone are high but reduce dramatically for ciprofloxacin in the presence of BPAA, whereas the IC_{50} for sparfloxacin in the presence of BPAA remains high.[62] There is also little change in the threshold value for levofloxacin.[59] These phenomena may relate to differing intermolecular interactions between fluoroquinolones and BPAA.[63]

Recent investigation, using a hippocampal slice model, has suggested that the convulsive potency of fluoroquinolones alone may relate more directly to the *N*-methyl-D-aspartate (NMDA) receptor.[64] This study has shown structure-dependent effects, indicating a much higher excitatory potential for agents such as trovafloxacin compared with existing drugs, for example ciprofloxacin and ofloxacin. This may explain the higher incidence of CNS effects seen in trovafloxacin postmarketing sur-

veillance data. The NMDA receptor is implicated in quinolone-induced seizures in animals, which can be prevented by NMDA antagonists.[65] Others have shown that trovafloxacin has higher potential for antagonism of [^{3}H] muscimol binding and consider that this may reflect an increased potential for interaction with NSAIDs. No clinical correlates of the latter have been observed in either registration or postmarketing surveillance studies. Further work is required before the recommendations for caution in coadministration of fluoroquinolones with NSAIDs[61] can be relaxed.

5. Phototoxicity

Fluoroquinolones are important causes of photoreactions. Over a 15-year period in Japan, fluoroquinolones were responsible for 142 out of 373 (38%) cases of drug-induced photosensitivity.[66] Both phototoxicity and photoallergy contribute to the picture. Fluoroquinolone photoallergy is dependent on photohaptenic substituents, which probably explain cross-reactivity and enhanced reactions when further exposure to different fluoroquinolones occurs in an individual.[66] For sparfloxacin, which is responsible for 41.5% of the fluoroquinolone-associated cases of photosensitivity in Japan, phototoxicity predominates.

Under the influence of UVA radiation fluoroquinolones induce cell-damaging phototoxicity, which varies in severity from mild sunburn to severe bullous reactions[67] and is probably due to the photogeneration of toxic free oxygen species.[68-70] Phototoxicity is most common (and severe) with 8-halogenated fluoroquinolones[16] and in particular with the 8-chloro derivatives, Bay y 3118 (withdrawn), clinafloxacin and sitafloxacin. Fleroxacin, a 6,8–difluoro compound, caused phototoxic reactions in 11 to 19% of patients receiving higher doses in early clinical trials.[71] Compounds without 8-halogenated substituents, particularly 8-methoxy derivatives (balofloxacin, moxifloxacin), have a much lower potential for phototoxicity.[72,73]

Mouse models can assist in predicting the phototoxic potential of fluoroquinolones.[74] For example, trovafloxacin produces a mild erythema in Balb/c mice at doses of 90 to 250 mg/kg, whereas lomefloxacin at 70 mg/kg produced a marked, persistent phototoxic response.[75] A comprehensive study of fluoroquinolones showed lomefloxacin and sparfloxacin to cause long-lasting erythema and oedema for the period of the study and enoxacin to cause erythema for similar periods.[76] Erythema following the use of ciprofloxacin, ofloxacin and grepafloxacin was mild and short-lived.[76] Data on sitafloxacin, comparing doses causing equivalent (50%) increases in ear thickness in Balb/c mice, indicate a similar phototoxic potential to that of enoxacin (70 to 80 mg/kg), compared with the higher potential of sparfloxacin, i.e. 50% increase at a dose of 28 mg/kg (Y. Niki, unpublished observation).

Human volunteer studies measuring photosensitising effect by changes in the minimum erythema dose of UVA during therapy showed second-generation agents such as ciprofloxacin and norfloxacin to have weak potential for phototoxicity which disappears within 4 weeks of treatment discontinuation.[77] Grepafloxacin[78] and trovafloxacin[79] had either equivalent or lesser phototoxic potential than ciprofloxacin, an agent which has rarely produced clinical phototoxicity.[1] Gatifloxacin, moxifloxacin and gemifloxacin exhibit phototoxicity indices that are no different from placebo.[80-82]

However, in clinical practice, some differences in phototoxic effect have been observed. Clinical phototoxicity was observed in 2% of patients in the grepafloxacin preregistration cohort[25] but in both trovafloxacin and moxifloxacin cohorts,[83] only 2 patients (<0.05%) developed treatment-related phototoxicity (mild sunburn) in series of almost 8000 and 4300 patients, respectively. The incidence was similar for levofloxacin, 1 out of 3640 patients, whereas the overall rate for sparfloxacin in North American experience was considerably higher at 7.9%.[15]

Data on clinafloxacin in serious infections in (presumably) hospitalised patients suggest a rate of 3.9% for significant photoreactions.[84] For this reason, plus its potential to cause significant

hypoglycaemia,[85] clinafloxacin may find only limited clinical application.

Specific patient groups may have a predisposition to fluoroquinolone induced phototoxicity. A questionnaire study in patients with cystic fibrosis in Canada reported symptoms of redness and/or blistering on sun-exposed areas in 52% of 42 patients receiving ciprofloxacin, rather higher than the 13 to 16% incidence encountered in previous trials of this and other fluoroquinolones in patients with cystic fibrosis.[86]

5.1 Photocarcinogenicity

Benign skin papillomas have been noted to appear in Albino mice after severe fluoroquinolone-induced, UVA-associated, phototoxic skin reactions[87] but certain fluoroquinolones, specifically lomefloxacin, are positively correlated with production of squamous carcinoma.[88] No cases in humans have been reported.

6. Cardiovascular Effects

Prolongation of the rate-corrected electrocardiographic QT interval (QTc), initially highlighted by effects observed with sparfloxacin, now appears highly likely to be a class effect. Data for the newer fluoroquinolones are summarised in table IV. Information on original second-generation fluoroquinolones is largely retrospective, but studies in rabbits show both dose-related increases in heart rate and, at very high doses (ciprofloxacin and lomefloxacin 300 mg/kg), ventricular tachycardia.[90]

Very few data associate fluoroquinolone-induced QTc interval changes with clinical phenomena. Overall, 2.9% of sparfloxacin patients had changes in baseline QTc interval compared with none of those receiving comparator agents.[89] Seven patients experienced serious cardiac effects (3 cases of ventricular tachycardia, 2 of tachycardia, 1 of asystole and 1 of death) in relation to sparfloxacin therapy during clinical investigations, all the patients had underlying cardiac disorders. Of the 3 patients with reversible ventricular tachycardia, 2 patients were receiving concomitant amiodarone. Two unexplained deaths, 1 from asystole in a patient receiving amiodarone and digoxin occurred during a 10-month period of surveillance in France.[89]

Various factors may predispose to drug effects on the QTc interval and generation of prearrythmias or arrhythmias. Perhaps prime amongst these is female gender, a predominance of both QTc effects and torsade de pointes being known to occur in women with both antiarrhythmic drugs and with macrolide antibacterials.[91] Investigation of moxifloxacin has shown no evidence of gender predisposition or of arrhythmia-related precursor events such as reverse rate depolarisation, QT dispersion or torsade de pointes. Data from moxifloxacin clinical trials have shown QTc interval prolongation equivalent in extent and incidence to that of comparators, but no associated arrhythmias or other cardiovascular events.[27]

No QTc phenomena were reported during the investigation of levofloxacin. However, a number of cases of torsade de pointes (frequency 0.3 per 100 000 treated patients) have emerged during postmarketing surveillance in the US.[7] The relationship to therapy is uncertain.

While cardiac effects in animals and QTc interval prolongation of varying degrees have been recorded with the newer compounds (table IV), clinically significant phenomena remain rare. Of 1406 patients receiving grepafloxacin, 2 (0.14%) developed tachycardia, although the cause-effect relationship is uncertain.[25] No patients receiving trovafloxacin in phase I to III clinical trials exhibited QTc intervals of >450 msec or changes of >60 msec.[45] and no cases of torsade de pointes or other potentially clinically significant phenomena have been observed.[26]

Therefore, either in animals or humans, most of the fluoroquinolones have been associated with, if not causally related to effects on cardiac rate and rhythm. This suggests that the phenomenon is a class effect. Therefore, the safety of other fluoroquinolones not previously reported to cause effects on the QTc interval or related clinical phenomena should not be assumed, especially should the pa-

Table IV. Reported corrected QT (QTc) interval phenomena and clinical correlates

Reported phenomena	Grepafloxacin[25]	Levofloxacin[7]	Moxifloxacin[40]	Sparfloxacin[89]	Trovafloxacin[45]
QTc interval prolongation (animals): oral or IV administration with dose implicated	Rabbits: 10-30 mg/kg IV (1 out of 4 at 30 mg/kg develop ventricular tachycardia)	No data available	30 mg/kg IV over 30 mins in dogs: QTc interval prolongation but no arrhythmia	Dogs: oral 25-45 mg/kg	No data available
QTc interval prolongation in humans: oral administration	Yes	Not observed in clinical trials	Yes	Yes	CPMP: 'none >450 msec or >50 prolonged'
QTc interval prolongation (humans): > upper limit of normal[a]	No data available	No reports available	Moxifloxacin: 9.5%[b] Comparators: 9.2%[b]	Yes	Not observed in clinical trials
QTc interval prolongation in humans: to >500 msec	No data available	No reports available	Moxifloxacin: 0.5% Comparators: 0.2%	10/880 pts with normal baseline	Not observed in clinical trials
Additive effects with drugs known to prolong QT interval	No data available	No reports available	Yes	Yes	No data
Risk factors/torsade de pointes	No reports available	Reported in PMS data from FDA (0.2/100 000 pts)	Positive in rabbit model (2 mg/kg/min) No human effects	Positive in rabbit model (2 mg/kg/min)	Not reported in PMS data from FDA
Significant clinical phenomena	No related CT phenomena. No deaths from arrhythmia	No related CT phenomena. No deaths from arrhythmia	No related CT phenomena. Two unrelated deaths from arrhythmia: 13 and 52 days after treatment	Three ventricular tachycardia: 0.4/100 000 pts, 2 related deaths	No related CT phenomena. No deaths from arrhythmia

a Upper limit of normal QTc interval: 450 msec in men, 470 msec in women.

b 6.4% (moxifloxacin) and 6.6% (comparators) respectively had prolongation of QTc interval at baseline.

CPMP = Committee of Proprietary Medicinal Products; **CT** = computed tomography ; **FDA** = US Food and Drug Administration; **IV** = intravenous; **PMS** = postmarketing surveillance; **pts** = patients.

tient be receiving other agents capable of producing QT prolongation.

7. Tendinitis and Tendon Rupture

Tendinitis and tendon rupture, most frequently affecting the Achilles tendon and bilateral in up to half of all patients, are rare complications of fluoroquinolone therapy.[92-94] Predisposing factors may include corticosteroid therapy[92,95] and, perhaps, renal disease, haemodialysis and transplantation.[96,97] Symptoms resolve usually within a few weeks but in 10% of patients they may persist for several months.[92] Magnetic resonance imaging is a useful diagnostic aid in early tendinitis[92] in symptomatic patients.[98]

Although initially it appeared that these effects were primarily associated with pefloxacin, it has become clear that this class effect may occur with most class members in use.[95] Prescription event monitoring studies in the UK, where pefloxacin is not available, have shown ofloxacin to feature somewhat more prominently in the total number of reports (11 patients), compared with ciprofloxacin (1) and norfloxacin (3).[29] However, a review of 421 patients with tendinitis collected in France confirmed that pefloxacin use was the major precursor, the frequency being 1 in 23 130 defined daily doses compared with 1 in 175 000 to 800 000 defined daily doses for other agents.[95] Isolated case reports continue to appear associated with ciprofloxacin,[99-101] the most frequently prescribed fluoroquinolone, and recent postmarketing surveillance data include cases following levofloxacin treatment.[7]

Fluoroquinolones should possibly be avoided in elderly patients, especially those receiving higher doses of corticosteroid therapy[95] and are contraindicated in athletes in training.[102]

8. Paediatric Use

The incidence and patterns of adverse reactions caused by ciprofloxacin in children are similar to those in adults. Gastrointestinal reactions accounted for 3.5% of a total of 10.9% reactions in almost 6500 children.[103] There are few data on the use of other fluoroquinolones in children in Western countries. However, in Japan norfloxacin (6 to 12 mg/kg/day for up to 7 days) is licensed for specific respiratory tract infections, urinary tract infections, skin infections and infective enteritis in children whose infection cannot be controlled with other therapy. High clinical efficacy rates of 94.5 to 92.5% are complemented by an overall adverse effect rate of 0.8% in studies involving almost 3500 children (Y. Niki, unpublished observation). Joint pain without arthritis was observed in 2 of the study participants.

8.1 Chondrotoxicity

The demonstration of severe cartilage erosions in weight-bearing, di-arthrodial joints of juvenile animals following exposure to prolonged high dose fluoroquinolone therapy,[1,5,104] resulted in the introduction of a moratorium on the use of these agents in children. Nevertheless, fairly extensive compassionate use of ciprofloxacin and other fluoroquinolones has indicated that prolonged use is well tolerated in paediatric patients and that there has been no significant evidence of chondrotoxicity in this group.[5]

Thus, an analysis of ciprofloxacin use on compassionate grounds in >1700 children in the UK, revealed no case of newly diagnosed acute arthritis or joint toxicity.[105] Indeed, no serious adverse effect directly related to ciprofloxacin was observed: existing haemolytic uraemic syndrome was considered to have worsened during therapy in 1 child. In a worldwide review of paediatric ciprofloxacin use, arthralgia occurred in 31 of 2030 treatments (1.5%).[106] Use of magnetic resonance imaging has shown no evidence of arthropathy occurring during therapy.[107,108]

More recently, a comprehensive review by Burkhardt and colleagues[86] in over 7000 children incorporating assessment of all available animal data has suggested that continued restriction of paediatric use on the grounds of possible chondrotoxicity may no longer be justified. Although 10 cases of transient arthralgia or joint swelling without long term sequelae were reviewed, most frequently in association with pefloxacin therapy, no single proven human case of joint toxicity could be attributed to fluoroquinolone therapy.

Fluoroquinolones are in widespread paediatric use in both Japan, where norfloxacin has a license for paediatric use,[109] and in developing countries for indications ranging from enteric fever, cholera and shigellosis.[110] No case of joint disease has been reported.

An International Commission of the International Society for Chemotherapy[111] has recommended that, while caution should remain, fluoroquinolones may be used in the following conditions when alternative safe and effective therapy is not available:

- broncho-pulmonary exacerbations of cystic fibrosis caused by *Pseudomonas aeruginosa*
- multi-resistant Gram-negative sepsis
- chronic suppurative otitis media
- epidemic shigellosis
- invasive salmonellosis (including typhoid fever)
- osteomyelitis
- prophylaxis in neutropenia resulting from anticancer therapy
- prophylaxis of meningococcal infection
- staphylococcal CNS shunt infection
- drug-resistant mycobacterial disease (in combination regimens).

Invasive disease caused by drug-resistant *Streptococcus pneumoniae* may become a major indication for the newer fluoroquinolones, which have markedly increased antipneumococcal potency. Prior to the demonstration of significant hepatotoxicity in adults, the FDA authorised trials of trovafloxacin in both paediatric meningitis and otitis media. The efficacy of trovafloxacin equalled

that of standard comparator in a large-scale study of meningitis[112] and it is possible that other third generation agents with similar antipneumococcal activity should be evaluated in this area.

Relaxation of guidelines in respect of chondrotoxicity does not, however, excuse lack of vigilance for other adverse effects of fluoroquinolones in children. For example, hypertension,[113] extrapyramidal syndromes[114] and benign intracranial hypertension[115] have been reported.

9. Interactions with Theophylline

Data on both second and third generation fluoroquinolones have been reviewed by Stahlmann and Lode.[14] Few of the newer agents have significant interactions [less than 4% increase or decrease in theophylline maximum plasma concentration after single-dose administration (C_{max}) or area under the plasma-concentration curve (AUC)], with the exception of grepafloxacin (28 to 33% increase in both parameters). The relative influences of newer fluoroquinolones on theophylline clearance in volunteers have been compared with earlier compounds.[116-118] Increases in AUC (%) were highest for enoxacin (84%) and the new compound grepafloxacin (33%), compared with tosulfoxacin and HSR-903 (24%), ciprofloxacin (22%), prulifloxacin (21%), ofloxacin (11%) and sparfloxacin/pazufloxacin (O%).

Subsequent studies confirm that, in contrast to other new fluoroquinolones, grepafloxacin coadministration reduces theophylline clearance by 50%.[119] Trovafloxacin coadministration, however, has no effect on the steady state pharmacokinetics of theophylline. No significant differences with placebo were observed in either C_{max} or AUC.[120] Neither moxifloxacin[121] nor gemifloxacin[122] affect the steady state pharmacokinetics of theophylline.

10. Conclusion

In many cases, fluoroquinolone adverse effects are structure related. Thus, halogen at the 8 position increases potential phototoxicity, whilst the 2,4 difluorophenyl substituent at the 1 position unique to temafloxacin and trovafloxacin may have played a role in the adverse effects that are specific to these agents. Understanding the structure-toxicity relationships may allow design of future compounds free of such effects. However, idiosyncratic and/or low frequency adverse effects may remain undetected until literally millions of doses have been administered, emphasising the need for rigorous, continuing postmarketing surveillance.

Important class effects described in our previous article[1] continue to occur. These include upper gastrointestinal upsets, CNS disorders, tendinitis, phototoxicity and joint toxicity (animals only). More extensive data are now available implicating fluoroquinolones other than sparfloxacin with QTc interval prolongation, though apparently without clinical significance. New potential class effects continue to appear, for example severe hepatic reactions and anaphylaxis, effects which are more common in patients with AIDs. Prescribers should be alert to other hazards. For example, pancreatitis may not be unique to trovafloxacin.

Despite rare, specific problems associated with individual fluoroquinolones, in general the class remains effective and well tolerated. However, expansion of use into specific groups, notably the sick elderly and children, may bring novel phenomena which must be anticipated and monitored.

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