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Potential Interactions of the Extended-Spectrum Fluoroquinolones with the CNS

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Abstract

The new generation fluoroquinolones – sparfloxacin, levofloxacin, grepafloxacin and trovafloxacin – have been designed to respond to the clinical need for extended antimicrobial cover in the face of increasing global microbial resistance. Their main focus is in the treatment of respiratory infections, particularly those acquired in the community.

CNS adverse effects, such as dizziness and headache, are known to occur relatively commonly with some fluoroquinolones and are not, in general, well tolerated by patients. The structural component of the fluoroquinolone molecule believed to be responsible for improved Gram-positive activity is also believed to be implicated in the production of CNS adverse effects, including those arising from drug interactions with theophylline and NSAIDs.

Inhibition of brain γ-aminobutyric acid (GABA) receptor binding appears to be a strong indicator of CNS activity, though *N*-methyl-*D*-aspartate receptor bind-

ing has also been implicated. In accordance with the results of these predictive studies, clinical trials have found sparfloxacin, levofloxacin and grepafloxacin to be associated with a low incidence of CNS events. Trovafloxacin has been found to be associated with a higher incidence of CNS events (particularly lightheadedness and dizziness) than the other 3 agents. Ongoing and future clinical studies will help to define the usefulness of the predictive models, as well as reveal the full CNS adverse event profile of these and other investigational fluoroquinolones.

The introduction of the first quinolone antibacterial, nalidixic acid, was an important advance in the treatment of infectious diseases. When this agent's derivatives, the fluoroquinolones, became available during the mid-1980s, the group's position among antimicrobial agents was secured. With their favourable pharmacokinetic properties and broad spectrum of activity, the fluoroquinolones, such as ciprofloxacin and ofloxacin, were widely used to treat a variety of infections, particularly those of the genitourinary, gastrointestinal (GI) and respiratory tracts.

On the whole, the fluoroquinolones are considered to have a relatively favourable tolerability profile, with mostly mild to moderate adverse effects consisting of upper GI tract reactions (e.g. nausea), nonspecific CNS events (e.g. dizziness) and phototoxicity.

Toxicity reports on cartilage damage to the weightbearing joints of young animals led to restrictions on fluoroquinolone use in pregnant women and children. However, some quinolones have been used in children for many years, with seemingly minimal joint sequelae, so this problem has been of little significance clinically. Achilles tendon disorders, including rupture and tendinitis related to quinolone treatment have been reported, although these are very rare.

A slight prolongation of the QT interval on the ECG has been observed with some fluoroquinolones, but this generally appears to be less than that reported for macrolides such as clarithromycin or erythromycin and has not generally been associated with cardiac arrhythmias.

Serious adverse events with fluoroquinolones are uncommon, although temafloxacin was approved in the US in January 1992 and subsequently withdrawn by the manufacturers in June 1992, following a number of deaths associated with anaphylaxis, haemolytic anaemia, renal failure, hypoglycaemia and hepatic failure. Recently, serious unpredictable hepatic adverse reactions have been described with trovafloxacin, including 9 cases where patients died or required a liver transplant. Recently, the Committee for Proprietary Medicinal Products (CPMP) has recommended suspension of trovafloxacin use for this reason.[1]

Nevertheless, fluoroquinolones as a class have been used for many years for the treatment of bacterial infections and they are generally well tolerated. They represent a valuable treatment option in an era when the efficacies of β-lactams and macrolides are increasingly being called into question.

The CNS effects of older fluoroquinolones are well documented, and represent the second most common type of adverse event;[2] overall incidence figures are estimated at: ciprofloxacin (≤2%), enoxacin (≤1.5%), pefloxacin (≤1%) and ofloxacin (≤1%).[3] Reported CNS effects include headache, dizziness, agitation, hallucinations, sleep disorders and, rarely, convulsions. These excitatory effects may be related to inhibition of brain γ-aminobutyric acid $(GABA)_A$ receptor binding.[4,5]

As a group, fluoroquinolones seldom cause convulsions when administered alone at therapeutic doses. However, the combination of certain fluoroquinolones with NSAIDs (notably enoxacin with fenbufen or its metabolite biphenylacetic acid)[6,7] appears to enhance the epileptogenic potential of the fluoroquinolone, a phenomenon likely to be the result of synergistic inhibition of $GABA_A$ receptor binding.[8] Furthermore, the coadministration of theophylline with certain fluoroquinolones may also give rise to convulsions via a similar mecha-

nism.[9,10] Thus, CNS events fall into 2 categories: those resulting from direct excitatory action within the CNS, and those mediated by coadministration of other drugs.

Although the withdrawal of temafloxacin in the early 1990s cast doubt over the use of this group of agents, the late 1990s has seen renewed interest in the fluoroquinolones.

The increasing incidence of global microbial resistance, particularly among respiratory pathogens, has led to clinical demand for more effective antimicrobials with extended spectra of activity. The most common respiratory pathogens; *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis*, all demonstrate increasing resistance to commonly prescribed agents, such as the ß-lactams. Even relatively modern fluoroquinolones, such as ciprofloxacin have been associated with clinical failures and breakthrough infections with *Streptococcus pneumoniae*, which reduces their usefulness in community-acquired pneumonia, where this pathogen is commonly implicated.[11-15]

Thus, the availability of new generation fluoroquinolones, such as grepafloxacin and trovafloxacin, which possess all the pharmacokinetic attributes of their predecessors, together with enhanced antimicrobial cover, particularly against Gram-positive pathogens, has been welcomed worldwide.

Despite this clinical need, the tolerability of fluoroquinolones continues to cause discussion and there is keen interest in the use of predictive *in vitro* and *in vivo* models to help define the likelihood of adverse events.

This article examines the potential of recently launched, extended-spectrum fluoroquinolones (sparfloxacin, levofloxacin, trovafloxacin and grepafloxacin) to induce CNS effects, and reviews clinical experience to date with these agents, particularly in respiratory tract infection (RTI). Investigational quinolones [e.g. moxifloxacin (BAY 12-8039) and DU-6859a] are referred to where data are available.

1. Extended-Spectrum Fluoroquinolones: a Profile

1.1 Clinical Role

With the possible exception of trovafloxacin, the most recently launched fluoroquinolones generally focus on the treatment of RTI (pneumonia, acute bacterial exacerbations of chronic bronchitis and sinusitis). For patients with community-acquired RTIs, most prescriptions for these new fluoroquinolones are likely to be written empirically in the primary care setting. Although relatively sick, many of these patients can be treated at home, thus it is vital for clinicians to be able to reassure them about adverse effects.

A recent pan-European survey of patient attitudes to antibacterial use found that CNS adverse effects, such as headache and dizziness, were the main source of patient concerns, particularly among older age groups.[16]

1.2 Structural Similarities and Differences

Design changes to the quinolone nucleus leading to the new extended-spectrum agents might well be expected to influence their adverse effect profile. Structurally, sparfloxacin and grepafloxacin most closely resemble ciprofloxacin, whereas in levofloxacin, which is the *S*-isomer of ofloxacin, the 4-quinolone nucleus is fused with an oxazine ring. All 5 compounds, however, contain a piperazine group at position C7, with sparfloxacin, levofloxacin and grepafloxacin containing an alkylated side-chain.

Trovafloxacin, on the other hand, is distinguished from other fluoroquinolones by a naphthyridone nucleus with a novel pyrrolidinyl side-chain at the C7 position (fig. 1).

Ultimately, these structural variations will account for the reported differences in these agents' microbiological activity, clinical efficacy and adverse effect profiles, though only ongoing and future preclinical and clinical studies will determine precisely how.

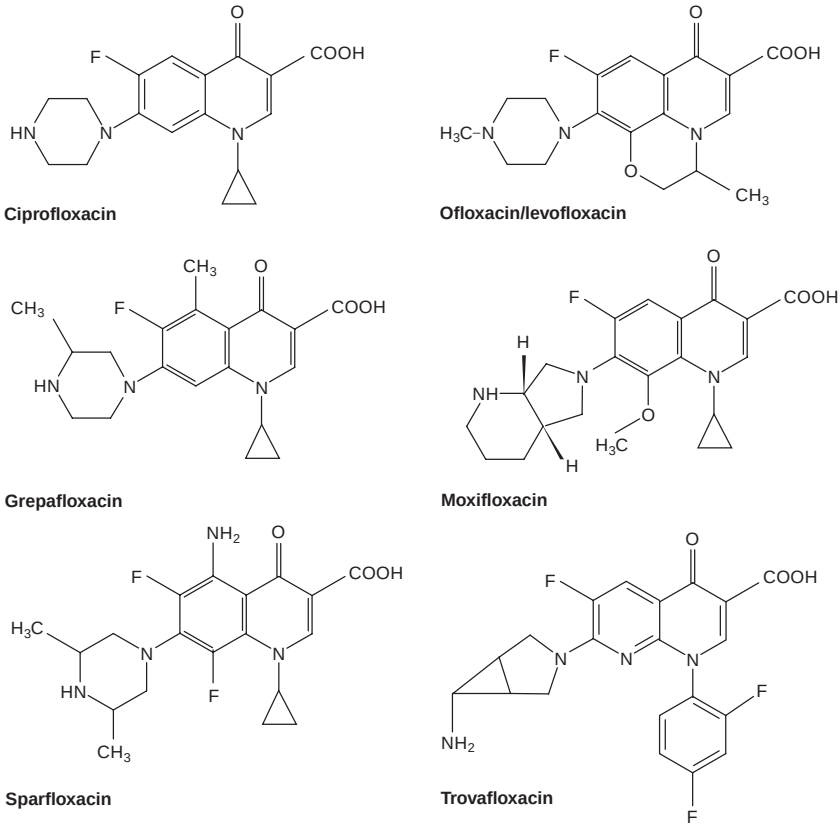

Fig. 1. Structure of the new quinolones compared with ciprofloxacin and ofloxacin – the C7 substituent is important in the determination of Gram-positive activity and CNS events, including those arising from drug interactions with NSAIDs and theophylline.

1.3 Lipophilicity and CNS Penetration

At the simplest level, structural changes are likely to affect the lipophilicity of a compound and thus, the extent of its penetration into the CNS. However, for the fluoroquinolones no clear relationship has yet been established between CNS penetration and CNS adverse events.

Pefloxacin shows extensive penetration into the CNS, yet is associated with a low incidence of CNS adverse events.[17] Interestingly, the concentrations of pefloxacin in the brain and serum have been shown to be similar, while CSF concentrations are lower (CSF/serum ratio: 0.3 to 0.5).[17]

To date, there is little information about penetration of new generation quinolones into the CNS. Both levofloxacin and grepafloxacin have low penetration into the CSF (CSF/serum ratios: 0.16 and 0.14, respectively),[18,19] as does the investigational fluoroquinolone, balofloxacin (CSF/serum ratio: 0.05).[20] On the other hand, trovafloxacin has a relatively high CSF penetration (CSF/serum ratio 0.25).[21]

At the time of writing, published data were not available on the human CSF penetration of moxifloxacin, but in a rabbit meningitis model, moxifloxacin achieved mean CSF/serum ratios, in normal and purulent CSF, of 0.5 and 0.8, respectively.[22]

Another study comparing sparfloxacin and ciprofloxacin found that both of these fluoroquinolones achieved similar brain and serum con-

centrations, while CSF concentrations were between 1.8 and 19.4-fold lower than those in serum or brain tissue.[23] The same study also investigated the potential of these 2 agents to interact with the brain GABA-ergic system. Although they behaved similarly in terms of CNS penetration, sparfloxacin did not have any activity as a GABA antagonist in the brain, in contrast to ciprofloxacin. It would, therefore, appear difficult to interpret the significance of CNS penetration in relation to CNS adverse effects without also considering the interaction of the quinolone with specific receptor systems in the brain.

2. Excitatory Potential

2.1 GABA Binding and Epileptogenic Activity

A detailed review of structure-activity and structure-adverse effect profiles by Domagala[24] has suggested that, while certain substituents at the C7 position may improve Gram-positive activity, excitatory CNS effects and drug interactions with theophylline and NSAIDs are also strongly influenced by the C7 side-chain substituent.

Studies by Akahane et al.[25] in mice have correlated the epileptogenic properties of fluoroquinolones with a high degree of binding to brain GABA receptors, and have found that the substituent at the C7 position is an important predictor of GABA binding. Akahane reported that quinolones which possess a piperazine substituted with 1 or more methyl groups at position C7 exhibited lower inhibition of GABA binding. This may be relevant for new, alkylated agents, such as levofloxacin, sparfloxacin and grepafloxacin.

Further studies have confirmed the involvement of the $GABA_A$ receptor in the epileptogenic activity of the fluoroquinolones,[19,20,26] and the enhancement of the epileptogenic effect of certain quinolones by synergistic inhibition with NSAIDs at the GABA receptor.[8] The quinolone and NSAID (or the fenbufen metabolite, biphenylacetic acid) are thought to form a hybrid compound.[27] Recent studies suggest that the formation of nitric oxide as a proconvulsant substance may result from activation of nitric oxide synthase by the fluoroquinolone/NSAID combination.[28,29]

2.2 Interactions with NSAIDs and Epileptogenic Activity

In an *in vitro* model using mouse synaptic membranes, grepafloxacin was found to have only moderate inhibitory activity at GABA receptors, and this activity was not enhanced in the presence of NSAIDs.[8] This observation was in contrast to the inhibitory activity observed with enoxacin, ciprofloxacin, norfloxacin and ofloxacin.[8] As a result, grepafloxacin was predicted to have a low epileptogenic potential. This theory was supported by *in vivo* data from a later study showing that convulsions were not induced in a mouse model during simultaneous administration of grepafloxacin and fenbufen or flurbiprofen.[30] Similar observations have been noted with sparfloxacin[23] and with the investigational quinolone, balofloxacin.[31]

A study involving coadministration of levofloxacin and biphenylacetic acid via intracisternal injection in mice[32] showed that the inhibitory effect of levofloxacin at GABA receptors was only weakly enhanced in the presence of biphenylacetic acid, with levofloxacin producing fewer convulsions than the other quinolones evaluated (ofloxacin and DR-3354).

In vitro data has recently become available for trovafloxacin in a study by Lambert et al.[33] which measured the inhibitory activity of various fluoroquinolones at $GABA_A$ receptors using rat brain synaptic membranes. When administered alone, trovafloxacin had unremarkable inhibitory activity at $GABA_A$ receptors, but in the presence of biphenylacetic acid the inhibitory effect of trovafloxacin was strongly enhanced, an effect which was not produced with the other new fluoroquinolones, levofloxacin and grepafloxacin (fig. 2). These data suggest that trovafloxacin is likely to have comparatively higher epileptogenic potential, although data from *in vivo* studies is needed in order to be able to draw firm conclusions.

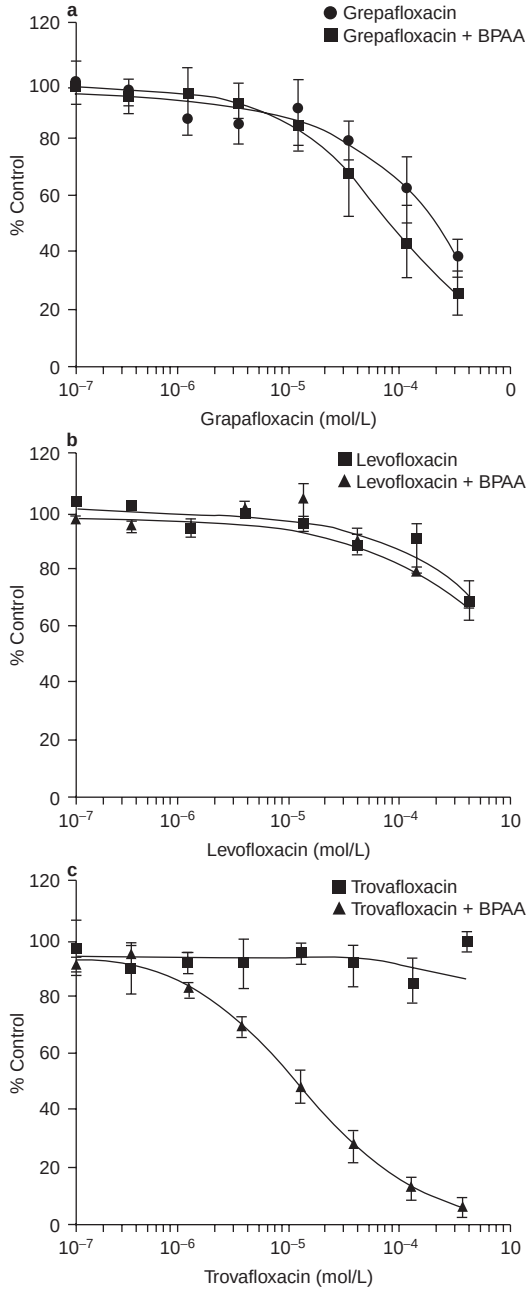

Fig. 2. Displacement of [3H]muscimol binding at γ-aminobutyric $acid_A$ receptors in rat synaptic membranes by: (**a**) grepafloxacin; (**b**) levofloxacin; and, (**c**) trovafloxacin in the absence and presence of biphenylacetic acid (BPAA), 1×10^{-5} mol/L. Data points are the mean of 3 independent assays, each performed in triplicate. Vertical bars indicate the standard error of the mean.[27]

Although it seems certain that inhibition of GABA binding plays a major role in the epileptogenic activity of fluoroquinolones, the observation that nalidixic acid, alone or in combination with biphenylacetic acid, is inactive in competitive radioligand binding studies with GABA,[4] suggests that other pharmacological mechanisms may also be involved. Nalidixic acid is associated with CNS events, particularly those of the visual senses. One recent *in vitro* study described below has investigated the involvement of the *N*-methyl-*D*-aspartate receptor.[34]

2.3 *N*-methyl-*D*-aspartate Receptors and Excitatory Potential

Schmuck et al.[34] used electrophysiological determination of evoked field potentials in the CA_1 pyramidal cell layer of the rat hippocampus slice to predict the convulsive potency of a variety of older and newer fluoroquinolones. At dose ranges reflecting brain concentrations achieved during therapeutic use, all of the agents tested increased amplitude of the field potential (the population spike amplitude) of the neurons in the CA_1 region in a dose-dependent manner (fig. 3). Some of the newer fluoroquinolones, notably trovafloxacin, demonstrated particularly high excitatory potency. The resulting excitatory potency ranking was as follows: ofloxacin < ciprofloxacin < nalidixic acid < moxifloxacin < fleroxacin < lomefloxacin < enoxacin < clinafloxacin < tosufloxacin < trovafloxacin < BAY 15-7828 < BAY X-9181.

Further experiments on the effects of Mg^{++} and MK 801 (which modulate and block the *N*-methyl-*D*-aspartate receptor–gated calcium channel, respectively), in combination with the fluoroquinolones, pointed to a direct involvement of the *N*-methyl-*D*-aspartate–gated ion channel as a target for the excitatory effect of fluoroquinolones. Although the authors were unable to draw conclusions regarding the specific relationship between structure and convulsive potential, an orientating experiment in the Rhesus monkey using moxifloxacin and BAY 15-7828 did show that the model was also relevant *in vivo*. Accumulation of clinical

data for the new fluoroquinolones should help to provide further insight into the predictive relevance of this model.

2.4 Interaction with Theophylline and Caffeine

The convulsive potential of fluoroquinolone-theophylline combinations is believed to be related to the inhibition of xanthine metabolism and toxic accumulation of theophylline via reduction in hepatic clearance. Theophylline, which is used as a bronchodilator, has a relatively narrow therapeutic index and toxic effects are more frequently observed if the serum concentration is >20 mg/L. Most commonly, these toxic effects manifest themselves as dizziness, headache, tremors and restlessness, with convulsions being observed in more severe cases.[35]

A structure-adverse effect study, using enoxacin and its derivatives, has shown that a 4′-nitrogen atom in the C7 piperazine group is likely to be involved in theophylline interactions, although fluoroquinolones with a bulky, alkylated side-chain on the piperazine group are likely to have reduced potential for interaction.[36] Not surprisingly, there are marked differences between quinolones; for example, enoxacin increases plasma theophylline concentrations by more than 100%, ciprofloxacin by 23% and pefloxacin by 20%.[9]

For the new-generation fluoroquinolones, studies in healthy male volunteers have shown that levofloxacin,[37] sparfloxacin[38] and trovafloxacin[39] have no appreciable effect on the steady-state pharmacokinetics of theophylline. An *in vitro* study using DU-6859a, an investigational fluoroquinolone, did reveal a minor interaction with theophylline.[40] However, when this agent was investigated in human volunteers, no adverse events were found at therapeutic concentrations, thus theophylline dosage might not need to be reduced during coadministration of this agent.[40] Grepafloxacin and clinafloxacin (the latter is still under investigation) have been found to lead to reduced theophylline clearance,[41,42] thus an adjustment in theophylline dosage is recommended if it is to be coadministered with these fluoroquinolones.

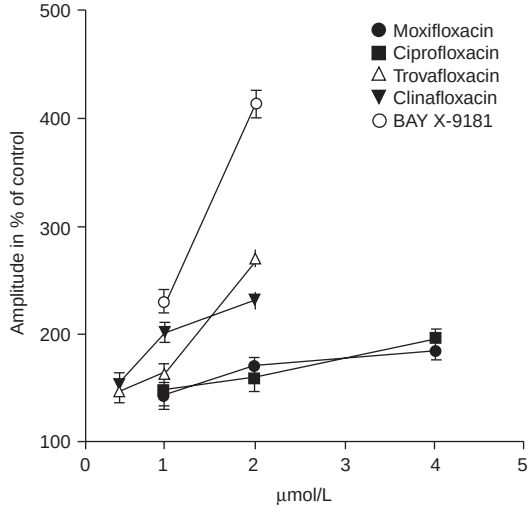

Fig. 3. Electrophysiological determination of evoked field potentials in the CA1 pyramidal cell layer of the rat hippocampus slice to predict convulsive potency of fluoroquinolones (reproduced from Schmuck et al.,[29] with permission).

Despite the differences between agents, because this type of interaction is considered to be a class effect, the prescribing information for most quinolones carries a warning regarding the necessity to monitor theophylline concentrations during coadministration of these agents.

Caffeine, like theophylline, is a methylxanthine and it is metabolised via the same cytochrome P450 1A2 route. Thus, quinolones that inhibit theophylline metabolism may also inhibit caffeine metabolism, with a concomitant potential for effects such as insomnia, restlessness, nervousness and tremors.[35]

2.5 Potential for Other CNS Effects

Although inhibition of GABA binding is widely believed to be a possible explanation for other observed CNS effects with fluoroquinolones (e.g. hallucinations, agitation and sleep disorders) there are no specific data in the literature to support this. Extrapolating to the clinical situation would suggest that quinolones with little or no inhibitory activity at GABA receptors (e.g. sparfloxacin and

grepafloxacin) would be expected to provoke these types of CNS effects infrequently. Although both of these quinolones actually do behave accordingly in clinical studies (see section 3), pharmacological studies will be needed to confirm that a mechanism involving the GABA receptor is involved.

3. CNS Tolerability Profile in Clinical Studies

3.1 Sparfloxacin

Sparfloxacin has been investigated principally in RTI, with particular emphasis on community-acquired pneumonia[43-48] and acute bacterial exacerbations of chronic bronchitis.[49,50] One study has evaluated sparfloxacin in sinusitis.[51] Over 2000 patients have participated in these trials. Dosage regimens were: for community-acquired pneumonia, sinusitis, and acute bacterial exacerbations of chronic bronchitis – 400mg loading dose then 200mg once daily; for acute bacterial exacerbations of chronic bronchitis a 200mg loading dose then 100mg once daily was also used. The major comparative trials have been European/International, though a number of small noncomparative Japanese trials have also been conducted. Comparators have been amoxicillin, amoxicillin/clavulanic acid, erythromycin, roxithromycin, ofloxacin, cefaclor and cefuroxime axetil.

Collated tolerability results from trials prior to 1997[52] show that, overall, around 5% of patients experienced CNS adverse events (headache and insomnia) with sparfloxacin, which was similar to or lower than the incidences with comparator agents. The acute bacterial exacerbations of chronic bronchitis study *vs* ofloxacin (400mg twice daily), showed an overall lower incidence of CNS effects with sparfloxacin (400mg + 200mg once daily).[48] For sparfloxacin (n = 395) and ofloxacin (n = 403), respectively, the incidences were: dizziness, 3 *vs* 2.5%; headache, 2.8 *vs* 1.5% and insomnia, 1.0 *vs* 11.4%.

3.2 Levofloxacin

Approximately 1000 patients have received levofloxacin in a number of recent comparative and noncomparative international and US trials in RTI,[53-60] genitourinary infection[61] and skin and soft tissue infection.[62,63] Comparator agents were ceftriaxone, cefaclor, cefuroxime axetil, ciprofloxacin, lomefloxacin and amoxicillin/clavulanate. For RTI, dosages were generally 500mg once daily, orally (or IV for community-acquired pneumonia), although a recent study in acute bacterial exacerbations of chronic bronchitis has evaluated a 250 mg/day dosage.[59] A twice-daily dosage regimen has also been evaluated in patients with community-acquired pneumonia.[56] Studies for the other types of infection have used dosages of 250 to 500mg once daily.

Although a relatively recent pharmacokinetic study involving 35 patients undergoing elective diagnostic bronchoscopy found high incidences of dizziness (8/35 patients; 23%) and headache (5/35 patients; 14%), after a single 500mg dose,[64] this has not been the case in clinical trials. Overall, the incidence of drug-related CNS adverse events recorded in clinical trials was found to be very low, at <1%. Reported events have included convulsions, lightheadedness, insomnia, anxiety, dizziness and headache. In general, comparisons with the other agents involved in the studies have not revealed any significant differences in terms of CNS events.

3.3 Grepafloxacin

Grepafloxacin has been given to over 3000 patients in US and UK phase II/III trials, mainly in acute bacterial exacerbations of chronic bronchitis[65,66] and community-acquired pneumonia,[67-70] at dosages of 400 or 600mg once daily. The trial comparators were the standard agents used in the indications, namely ciprofloxacin, amoxicillin, clarithromycin and cefaclor. Grepafloxacin (400mg single dose or once daily for 7 days) has also been compared with doxycycline and cefixime in genitourinary infections.[71-73]

In clinical trials conducted for registration, treatment-related CNS events (headache and dizziness) occurred in less than 5% of all patients receiving grepafloxacin, and there were no reports of convulsions.[74] In a study which compared ciprofloxacin 500mg twice daily with grepafloxacin 400mg or 600mg once daily for acute bacterial exacerbations of chronic bronchitis, there were no statistical differences between the 2 drugs in the incidences of dizziness and insomnia.[66]

A recent case-report study carried out in Germany[75] supports these results and has shown that, in everyday practice, the incidence of CNS effects with grepafloxacin is very low. Data from more than 9000 patients, mainly diagnosed with acute bacterial exacerbations of chronic bronchitis and community-acquired pneumonia, showed that dizziness was reported by only 25 patients (0.3%) and headache by only 16 patients (0.2%).

3.4 Trovafloxacin

Lightheadedness, dizziness and headache have been reported in single and multiple dose tolerability and pharmacokinetic studies conducted with trovafloxacin.[76,77] In addition, clinical studies suggest that adverse effects involving the CNS are the most common adverse events with this drug.[78-81] The reported incidence of dizziness varied between studies according to a number of factors including dosage and indication.

Three recent studies in ambulatory[79] or hospitalised[79] patients with community-acquired pneumonia and in nosocomial pneumonia,[81] in which trovafloxacin was given to 526 patients at a dosage of 200mg once daily[1] for 7 to 14 days, confirmed that CNS adverse events occur most commonly, with dizziness, headache and lightheadedness all being reported. In the ambulatory community-acquired pneumonia study by Sullivan et al.,[79] dizziness/lightheadedness was experienced by 10% of patients receiving trovafloxacin, compared with only 2% of patients treated with the comparator agent, clarithromycin. The same percentage of patients in each group (3%) experienced headache.

In the entire trovafloxacin clinical trials database of over 6000 patients, dizziness occurred in 3% of patients treated with 100 mg per day, increasing to 11% among patients treated with 200mg perday.[78] The US prescribing information for trovafloxacin shows the combined data for 3259 patients receiving oral trovafloxacin 200mg once daily and indicates that 11% have experienced dizziness, 4% lightheadedness and 5% headache. As already mentioned, the CPMP has recommended suspension of trovafloxacin use because of increasing concerns about hepatic toxicity (see introduction).

3.5 Investigational Fluoroquinolones

Several new members of the fluoroquinolone group are currently in various stages of clinical investigation, though few published data are available. One study with sitafloxacin (DU-6859a)[82] and one single-dose study with clinafloxacin[83] have shown these drugs to be well tolerated, with seemingly no significant incidence of CNS adverse events compared with placebo.

An analysis of the tolerability profile of moxifloxacin from 20 trials showed that dizziness and headache were reported in 2.9 and 2% of patients respectively.[84] For the other investigational agents, large comparative clinical trials will be necessary to obtain a more accurate picture of the adverse event profiles of these agents. To date, no information has been published on the incidence of CNS adverse events with gatifloxacin (AM-1155).

4. Conclusions

For any new cluster of agents with similar indications, clinicians need to make a therapeutic selection on a rational basis, achieving a balance largely between efficacy and tolerability. For the extended-spectrum fluoroquinolones, which will largely be used empirically in the community, it is important to select an agent which causes mini-

1 Patients with nosocomial pneumonia and hospitalised community-acquired pneumonia were first given alatrofloxacin IV 300 mg/day prior to receiving oral trovafloxacin.

mum disruption to patients, while maximising clinical efficacy and microbiological spectrum of activity. CNS effects, such as lightheadedness and dizziness, are not generally well tolerated by patients, although these have been found to occur commonly with some quinolone antibacterials.

Although design changes to the quinolone nucleus to produce the new, extended-spectrum agents may have been expected to affect their CNS profile, sparfloxacin, levofloxacin and grepafloxacin have all been associated with a low incidence of CNS adverse events in clinical trials which is encouraging in terms of their therapeutic potential in the community. However, the usefulness of sparfloxacin may be limited by its phototoxic potential.[85]

Seemingly, an exception to the CNS tolerability of the extended-spectrum fluoroquinolones may be trovafloxacin; so far, this agent appears to be associated with a higher incidence of CNS events than comparator agents or other extended-spectrum quinolones. It is interesting to note that, in predictive models involving quinolone binding to GABA and *N*-methyl-*D*-aspartate receptors, trovafloxacin was found to be correlated with a greater likelihood of excitatory potential than other new agents.

Although the use of predictive models is at a relatively early stage, ongoing development will be welcomed and accumulation of clinical data for the new fluoroquinolones should help to provide further insight into the relevance of the various models.

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