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Special Issue – Lomefloxacin: a clinical appraisal

Guest Editor
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Introduction

Lomefloxacin: a once-a-day quinolone

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(Accepted 17 September 1992)

The introduction of norfloxacin and pefloxacin marked the advent of the new more powerful quinolones, forerunners of a group of drugs now widely used – particularly for treatment of urinary tract infections and out-patient lower respiratory tract infections. Quinolones are also proving of value for gonococcal infections and those gastrointestinal infections that require antimicrobial therapy.

Lomefloxacin was discovered in Japan; it has a methyl-piperazinyl group which means that in addition to a wide spectrum of activity, and a high potency, it is almost completely absorbed, and has a prolonged (7–8 h) half-life in the blood allowing the once-a-day dosage.

The papers presented here arise from work around the world as part of an ambitious clinical trials program conducted outside of Japan by Searle and complement those already published describing the trials carried out in the USA (*Am J Med 1992;92:Suppl 4A*) to provide readers with an overview of the efficacy, safety and potential clinical uses of lomefloxacin. Such a program unites scientists and doctors from many countries into one large group. This program was of interest not only in evaluating the properties of the drug, but also in reflecting problems and attitudes in different countries. The two international symposia at which these papers were presented allowed for wide-ranging discussions between participants from all over the world.

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The initial clinical program was focused on urinary tract and lower respiratory tract infections. While the use of quinolones for the urinary tract is now well established, that for lower respiratory infections has always been subject to doubt with regard to the efficacy against *Streptococcus pneumoniae*. The studies reported by Yernault and Russell are therefore of interest. Although there was some selection of patients to exclude those with community-acquired pneumonia, many were unselected. Lomefloxacin eradicated pneumococci in 70% of patients with acute exacerbations of chronic bronchitis from whom this organism was recovered. In exacerbations caused predominantly by Gram-negative flora, lomefloxacin given once a day was superior to amoxicillin given three times daily.

Also of note is the paper on treatment of diarrhea by Seto, Lau, Gotuzzo and Carillo from Hong Kong and Peru. For those enteric infections where an antibiotic may be indicated the quinolones offer significant clinical benefits; it is pertinent to note that lomefloxacin has been used with success for cholera in South America.

To date quinolones have rarely been used for skin and soft tissue infection in which the infecting organisms are predominantly Gram-positive. However, the paper by Amaya-Tapia et al. implies that treatment of the Gram-negative bacteria often found in association with such infections may cause an improvement, and that the quinolones have a role in this common affliction.

This special issue also includes two important reviews from New Zealand. Bailey has reviewed the

short-term therapy for acute uncomplicated urinary tract infection, noting that 3-day courses are now well established and holding out the hope of single-dose therapy. Finally, Robson has provided an authoritative review of the pharmacokinetics of quinolones – into which lomefloxacin fits as a very 'clean' drug. The latter review also includes mention of the first data on repeated doses of lomefloxacin in renal failure – obviously a topic of interest for a drug with renal excretion and a long half-life.

These studies show that lomefloxacin can compete satisfactorily with conventional therapies for some common infections. The convenience of a once daily dosing should ensure continuing interest in this drug.

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Review

Quinolone pharmacokinetics

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(Accepted 18 September 1992)

Fluoroquinolones have broad antibacterial spectra and are active against most Gram-negative and many Gram-positive species. They exhibit excellent oral bioavailability, extensive tissue penetration, low protein binding, and a long elimination half-life. This review compares and contrasts the pharmacokinetics of some quinolone antibiotics – especially pefloxacin, ciprofloxacin, enoxacin, norfloxacin, ofloxacin, fleroxacin and lomefloxacin – in terms of their absorption, distribution, metabolism, elimination, and interactions with other drugs and with food. In addition, the pharmacokinetics of these agents in the elderly and in patients with renal or hepatic impairment is discussed. The fluoroquinolones are established as a major class of antibiotics in the treatment of infections but pharmacokinetic factors should be considered when deciding on the most appropriate of these agents to use in individual patients.

Key words: Absorption; Distribution; Metabolism; Elimination; Interactions; Safety

Introduction

The fluoroquinolone group of antimicrobial agents has a broad antibacterial spectrum and is active against most Gram-negative and many Gram-positive bacteria. The pharmacokinetics of these drugs has been extensively studied across a range of subjects including healthy young volunteers, the elderly, patients with renal impairment, and patients with liver disease. The fluoroquinolone group exhibits excellent oral bioavailability, extensive tissue penetration, low protein binding, and a long elimination half-life. There are, however, significant differences between individual fluoroquinolones in their oral bioavailability, route of elimination, elimination half-life, and drug interactions. This review will compare and contrast the pharmacokinetics of some of the quinolone group, specifically pefloxacin, ciprofloxacin, enoxacin, norfloxacin, ofloxacin, fleroxacin, and lomefloxacin.

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Absorption

As a group, the fluoroquinolones demonstrate rapid absorption following oral administration. After oral administration, the time (T_{max}) to reach

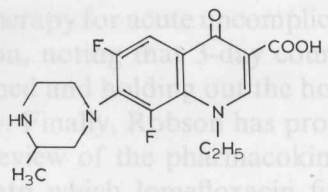

Fig. 1. Structure of lomefloxacin.

maximum concentration (C_{max}) is approximately 0.5–3.0 h [3]. Lomefloxacin and ciprofloxacin peak concentrations are achieved after 1–2 h. There are variations between the dose and maximum plasma concentrations achieved. After a single 400 mg oral dose of norfloxacin the mean C_{max} is in the range 1.4–1.6 mg/l; however, bioavailability decreases with increasing dose and the average is approximately 70% [20]. Similarly, ciprofloxacin achieved a C_{max} of 2.5 mg/l after a 500 mg dose but significant differences have been demonstrated in the bioavailability of different dosage forms of the drug [7]. By contrast, fleroxacin achieved a mean C_{max} of 5–6 mg/l following a single 400 mg dose and pefloxacin a C_{max} of 6.0–6.5 mg/l following a 600 mg dose [27]. Ofloxacin also achieved a higher mean C_{max} value of 3.2–5.0 mg/l following a 400 mg dose [10]. Dose-proportionality occurred with increasing oral doses of the drug. The absolute bioavailability of ofloxacin approached 100%. This is also the case for lomefloxacin which demonstrates a good correlation between dose and C_{max} over the range 100–800 mg following single-dose oral administration; the C_{max} achieved after a 400 mg dose is 3.0–5.2 mg/l [43].

Effect of food

The absorption of fluoroquinolones is only slightly affected by food. Food does not reduce the absorption of ofloxacin, ciprofloxacin, pefloxacin, and lomefloxacin to a clinically important extent. There are, however, differences in the rates of absorption for the different quinolones. The C_{max} for ofloxacin is reduced to 69% and T_{max} is prolonged by 203% compared with the fasting state [19]. In contrast, the effect of food on lomefloxacin absorption is small with the area under the curve (AUC) reduced to 91–94%, C_{max} reduced to 83–87% and T_{max} prolonged to 169–172%. The type of meal (standard versus high fat) does not significantly affect the magnitude of this interaction of food with lomefloxacin absorption [21]. The clinical significance of the effects of food on quinolones is speculative but it is likely that a large reduction in C_{max} may result in lower efficacy.

Accumulation has been reported following multiple doses. In the case of ofloxacin, there is a small degree of accumulation of the parent drug. However, for those quinolones where metabolites have been identified, enoxacin, pefloxacin and ciprofloxacin, accumulation of metabolites can occur. The degree of accumulation is linked to the level of renal impairment. No accumulation of lomefloxacin has been reported after multiple dosing in healthy volunteers and C_{max} values approximate those measured after single dosing.

Distribution

The degree of protein binding with the newer fluoroquinolones is low: approximately 30% with ciprofloxacin, 20% with ofloxacin, and 10% with lomefloxacin. The apparent volume of distribution of ciprofloxacin is large, 1.74–5.00 ml/kg [42]. Lomefloxacin has an apparent volume of distribution of 1.7–2.5 ml/kg [43] and the value for ofloxacin is 1.3–1.8 ml/kg. The fluoroquinolones demonstrate excellent and relatively comparable tissue penetration. Peak concentrations in prostatic and gynecologic tissue, bile, liver and gall bladder tissue, and pancreatic fluid are several times those of the serum concentrations. Ciprofloxacin concentrations 10 times those of plasma concentrations have been reported in bile and prostatic tissue [41]. The concentrations of lomefloxacin, ciprofloxacin, and ofloxacin in lung tissue and bronchial mucosa are also several times the plasma concentrations. The concentrations of ofloxacin and lomefloxacin in sputum and bronchial secretions were equal to plasma concentrations. The concentrations of ciprofloxacin in sputum and bronchial secretions were significantly lower than the plasma concentration. Lomefloxacin and ciprofloxacin readily penetrate the cornea, iris, ciliary body, and serum of the eye. Ofloxacin and ciprofloxacin also show good penetration into the

central nervous system. There is experimental evidence that small amounts of lomefloxacin cross the blood– brain barrier and enter the extracellular space [39].

Metabolism and elimination

The individual fluoroquinolones differ markedly in their degree of metabolic biotransformation. The degree of metabolism explains the differences observed in the total body clearance and elimination half-life of these drugs.

Pefloxacin has a high degree of metabolism (60–85%) with less than 10% being recovered as unchanged drug in urine. Approximately 40% is found as two major metabolites, the *N*-desmethyl metabolite which is active and the *N*-oxide metabolite which is inactive [25]. As do the newer quinolones, pefloxacin has a long terminal half-life of between 11 and 12 h in normal subjects. At the other end of the spectrum, ofloxacin is known to undergo almost no metabolite biotransformation with approximately 70–80% of the dose being renally excreted as unchanged drug and only 4% of a dose detected as metabolites [24]. Ofloxacin is characterized by a long elimination half-life ($t_{\frac{1}{2}}$=7–8 h). Similarly, lomefloxacin has an elimination half-life of 6–9 h with renal excretion accounting for 70–80% of the clearance. Very low concentrations of five metabolites of lomefloxacin have been identified; two of these have minimal antibacterial activity [28]. Fleroxacin also has a long half-life (9–12 h) with 60–85% of the dose recovered (50–75% as unchanged drug by glomerular filtration and tubular excretion). The two metabolites, *N*-desmethyl and the inactive *N*-oxide, account for 5–10%. The *N*-desmethyl metabolite is known to exhibit a 50% longer mean $t_{\frac{1}{2}}$ than the parent drug [44].

The elimination half-life of enoxacin is 4–6 h with metabolism accounting for 50% of the clearance; oxoenoxacin is the major metabolite. As with fleroxacin, enoxacin is eliminated by the kidney by both glomerular filtration and active tubular secretion [5].

Non-renal clearance mechanisms account for about one third of the elimination of ciprofloxacin. It has been suggested that hepatic extraction and excretion into the bowel are significant non-renal pathways. Four major metabolites have been identified which account for 10–20% of the dose, while 45–60% of the drug is excreted unchanged in urine by glomerular filtration and active tubular secretion [9]. The $t_{\frac{1}{2}}$ of ciprofloxacin is 3–5 h.

Norfloxacin has a terminal half-life of 3.5–6.5 h. Six metabolites have been identified, one of which has antibacterial activity. About 30% of the dose is recovered unchanged in the urine with urinary excretion of the metabolites accounting for less than 10% of the dose [1].

Drug interactions

Two important drug interactions have been identified with the new fluoroquinolone antibiotics. Firstly, there is decreased fluoroquinolone bioavailability due to interference with gastrointestinal absorption when co-administered with magnesium-aluminum antacids. Secondly, inhibition of theophylline metabolism occurs when fluoroquinolones and theophylline are administered concomitantly.

Effect of antacids

In 1985, the interaction between ciprofloxacin and an antacid containing magnesium and aluminum (Maalox®) was first reported [18]. This antacid reduced the ciprofloxacin C_{max} from 1.7 mg/l to 0.1 mg/l, and the renal excretion of unchanged drug from 24% to 2% of the administered dose. All the newer fluoroquinolones investigated since 1985 have also been shown to interact with antacids containing magnesium and aluminum. As measured by bioavailability, the magnitude of the quinolone-Maalox® interaction varies: ciprofloxacin reduces to 18% of the fasting values [30], norfloxacin reduces to 14% [31], and lomefloxacin reduces to 50% of the fasting values [11]. The extent of the interaction is also dependent upon the time that the antacid is administered. Schentag et al. [40] and Nix et al. [31] have investigated methods to minimize the ciprofloxacin-Maalox® interaction. Absorption is not significantly affected when Maalox® is administered within the 6 h before or 2 h after ciprofloxacin dosing. Administration of Maalox® within 4 h before

ciprofloxacin significantly reduces the latter's bioavailability. Both authors concluded that the most practical advice was to avoid the use of magnesium/aluminum-containing antacids in patients treated with ciprofloxacin.

The window of the interaction also varies between the different fluoroquinolones. Lomefloxacin can be administered within ± 2 h of Maalox® without a clinically significant interaction, whereas ciprofloxacin interacts within −4 h to +2 h.

Two hypotheses for the mechanism of the interaction have been suggested. An initial hypothesis was that as the quinolones are amphoteric with isoelectric points between pH 6 and 8, an increase in pH could reduce the dissolution and hence reduce absorption. The alternative hypothesis was that the quinolones formed a quinolone-metal complex resulting in decreased solubility. If this latter hypothesis were correct then the possibility of other divalent cations also forming quinolone-metal ion complexes exists.

The two hypotheses were investigated by a number of authors for a variety of quinolones. Several studies excluded the pH hypothesis. Nix et al. [30] reported in 1989 that pretreatment with ranitidine did not alter the bioavailability of ciprofloxacin. Similarly the bioavailability of lomefloxacin when administered 1 h after ranitidine 50 mg i.v. did not reduce its bioavailability [29]. In comparison, the bioavailability of enoxacin was reduced by 25% with ranitidine administration [13]. Apart from enoxacin, these results suggest that a pH increase to 5 or 6 is not sufficient to reduce the absorption of the fluoroquinolones. The lack of interaction with ranitidine supports the hypothesis that the antacid-fluoroquinolone interaction is not primarily due to a pH-related phenomenon.

Sucralfate, an anti-ulcer medication, is a complex of aluminum hydroxide and sulphated sucrose. Sucralfate does not affect gastric pH and acts by coating the ulcer surface. The anion of sucralfate binds to the positively-charged protein molecules in the ulcer releasing free aluminum ions. The high local concentration of aluminum cations reduces the bioavailability of the quinolones. Co-administration of sucralfate reduces norfloxacin bioavailability by 98% [32] and ciprofloxacin bioavailability by 87% [12]. Administration of sucralfate 2 h before norfloxacin, ciprofloxacin and lomefloxacin results in a 43%, 30% and 25% reduction in relative bioavailability, respectively [29].

The quinolone interaction with sucralfate and with aluminum-magnesium-containing antacids but not with ranitidine strongly supports the hypothesis that the metal ions are involved in reducing quinolone bioavailability. The mechanism of the quinolone-cation interaction is probably chelation between the metal and the 4-oxo and adjacent carboxyl group. The 4-oxo and adjacent carboxyl groups are required for antimicrobial activity. It is probable that all the quinolones will interact with these cations although the extent of the interaction does vary between the individual drugs.

Other cations

Other preparations containing cations, including iron and calcium, may also interact with quinolones. Sahai et al. [37] and Polk et al. [33] have investigated the effects of calcium carbonate, ferrous sulfate and zinc on the bioavailability of ciprofloxacin. Calcium carbonate administered three times daily with meals reduced the bioavailability of ciprofloxacin by 40% [37]. Ferrous gluconate, 325 mg three times daily and multivitamin tablets containing zinc reduced ciprofloxacin bioavailability by 65% and 24%, respectively [33].

Effect of methylxanthine metabolism

Quinolone-methylxanthine interactions

The newer fluoroquinolones, enoxacin, pefloxacin, ciprofloxacin and ofloxacin, have all been shown to inhibit the metabolism of theophylline. Wijnands [45] suggested that the chemical structures of enoxacin, ciprofloxacin and the methyl-substituted analogs, pefloxacin and ofloxacin, precluded the parent drug being the cause of the inhibition of theophylline metabolism. There are differences in the metabolic clearance of these newer quinolones, especially in the formation of the 4-oxo metabolite; ofloxacin shows only traces of the 4-oxo metabolite.

Wijnands et al. [45] also suggested that the inhibition of theophylline metabolism by the quinolones

was due to the formation of the 4-oxo metabolite. The evidence supporting this theory was firstly, that the 4- oxo piperidine group is chemically similar to the N_1-N_3 portion of the dimethylxanthine structure and, secondly, that the extent of inhibition of theophylline metabolism correlated with the urinary recovery of the 4-oxo metabolite for enoxacin, ciprofloxacin, and pefloxacin. Consistent with this hypothesis is the fact that nalidixic acid does not inhibit theophylline and is not metabolized to the 4-oxo metabolite. There are exceptions, however; pipemidic acid does not form a 4-oxo metabolite but is a potent inhibitor of theophylline metabolism.

Harder et al. [15] suggested an alternative hypothesis that the methylxanthine interaction is coincident with the naphthyridine (enoxacin) or pyrido-pyrimidine (pipemidic acid) structure bound to a piperazine ring. The quinolones, which have the greatest impact on theophylline clearance, are therefore more stereochemically similar to theophylline. Substitutions at position 8 on the quinolone nucleus would result in steric hindrance and decrease the similarity in structure with theophylline.

The latter hypothesis is supported by in vitro interaction studies with caffeine [14], theophylline [38], and the quinolones which demonstrate competitive inhibition consistent with the in vivo studies. In addition, preincubation of the quinolones with human liver microsomes produced identical results suggesting that the parent compound and not the metabolite(s) is responsible for inhibition of theophylline metabolism. In vivo and/or in vitro studies with the 4-oxo quinolone metabolites are required to clarify which hypothesis is correct.

Quinolone-theophylline interactions

The magnitude of the reduction in theophylline clearance varies between the fluoroquinolones, with a 64% decrease in theophylline clearance with enoxacin [36,45] and a 30% decrease with ciprofloxacin or pefloxacin [2,45].

To identify which theophylline metabolic pathways (1-demethylation, 3-demethylation and 8-hydroxylation) were inhibited by fluoroquinolones, a steady-state study in nine healthy volunteers was performed with ciprofloxacin [35]. In addition, lomefloxacin, a newer fluoroquinolone, which is substituted at the 8 position and which does not form a 4-oxo metabolite, was included to test the hypothesis that the quinolones without a 4-oxo metabolite do not inhibit theophylline metabolism.

Ciprofloxacin treatment reduced mean plasma theophylline clearance by 27%, consistent with the 30% reduction in theophylline clearance reported previously [14,45]. Clearance by all three metabolic pathways was reduced, although the reduction via the 8-hydroxylation pathway (24%) was less than the reduction via the 1-demethylation (37%) and 3-demethylation (42%) pathways. The difference in reduction for clearance via the 8-hydroxylation pathway was not statistically different ($p > 0.05$) from the reduction in clearance via the 1-demethylation and 3-demethylation pathways.

Lomefloxacin treatment had no effect on theophylline metabolism, consistent with the hypothesis that it is the 4-oxo metabolites of the fluoroquinolones which inhibit theophylline metabolism [45]. Lomefloxacin, unlike ciprofloxacin, does not form a 4-oxo metabolite. In addition, as lomefloxacin is substituted in the 8 position, the lack of interaction could also be consistent with the alternate hypothesis that the parent compound is responsible for the inhibition of theophylline metabolism.

The quinolone-theophylline interactions suggest that the reduction in theophylline clearance induced by enoxacin, ciprofloxacin, pefloxacin, ofloxacin, and pipemidic acid is of clinical importance.

Quinolone-caffeine interactions

Caffeine is metabolized by primary metabolic pathways similar to theophylline which are cytochrome P-450-mediated. As discussed, any drug inhibiting the cytochrome P-450s involved in theophylline metabolism would be expected to similarly affect caffeine metabolism.

Lomefloxacin does not inhibit theophylline or caffeine. A double-blind, two-way crossover, steady-state study by Healy et al. [16] in which 16 healthy volunteers received either lomefloxacin 400 mg daily or placebo with caffeine 200 mg daily for five days, confirmed that lomefloxacin did not alter the disposition of caffeine.

In contrast, ciprofloxacin [17] inhibited caffeine by 33%. The reduction in caffeine clearance was ac-

companied by a 43% reduction in the appearance of paraxanthine, the major metabolite, suggesting that the reduction in caffeine clearance is due to inhibition of the cytochrome P-450 isozyme involved.

Special population pharmacokinetics

The effect of renal function on quinolone pharmacokinetics

The degree to which renal insufficiency affects the pharmacokinetic profile of the new fluoroquinolones depends on the route of elimination. Therefore pefloxacin, which is extensively metabolized, demonstrates no significant change in total clearance in patients with renal failure. In addition, unchanged drug does not accumulate in patients with renal impairment. There is, however, a four- to six-fold accumulation of the two main metabolites in chronic renal failure patients [22]. No modification in the dosage regimen is required for patients with renal insufficiency.

Ciprofloxacin plasma concentrations are higher in chronic renal failure patients with the elimination half-life and AUC in severe renal failure being twice that of healthy volunteers. A wide range of C_{max} and $t_{1/2}$ has been reported in patients with severe renal failure. This variability is thought to be due to differences in individual hepatic clearances. Dosage adjustment is appropriate in order to achieve the same concentrations of ciprofloxacin. Enoxacin, which is 50% cleared via the kidney, demonstrates a marked variation in steady-state concentration in relation to renal function. In one study, concentrations ranged from 0.44 mg/l in normal subjects to 4.07 mg/l in chronic renal failure patients. In addition, the terminal half-life ranged from 6 h in normal subjects to 30 h in chronic renal failure patients [5]. Dosage adjustment is required in severe renal failure. Similarly a four-fold increase in the elimination half-life of norfloxacin has been reported in patients with severe renal impairment. Linear relationships exist between total clearance and creatinine clearance, and between renal clearance and creatinine clearance. This is also the case for fleroxacin. In both cases, up to a 50% reduction in dosage is recommended for those patients with a creatinine clearance of < 20–30 ml/min. Due to the high degree of renal excretion, ofloxacin and lomefloxacin show up to a five-fold increase in AUC and terminal half-life in severe renal failure patients. This increase is particularly pronounced as soon as creatinine clearance falls below 20 ml/min, $t_{1/2}$ being up to 48 h and renal clearance < 0.6 l/h. Dosage adjustment is therefore required. The effects of renal impairment on lomefloxacin clearance were evaluated after a single 400 mg oral dose [4] and at steady-state in patients with varying degrees of renal impairment [34]. Both studies showed a significant relationship between creatinine clearance and lomefloxacin plasma clearance.

Twenty subjects (13 males, seven females) were studied at steady-state. Subjects were divided into four groups of five; five with a glomerular filtration rate (GFR) > 90 ml/min, five with a GFR of 60–90 ml/min, five with a GFR of 30–60 ml/min and five subjects with a GFR of < 30 ml/min (not on dialysis). Subjects received 200 mg lomefloxacin for seven days. On day 7, after an overnight fast, steady-state pharmacokinetic parameters were evaluated. There was a significant relationship between creatinine clearance versus lomefloxacin plasma clearance ($r = 0.86, p < 0.05$) and lomefloxacin renal clearance ($r = 0.77, p < 0.05$).

The clearance of all quinolones is low by hemodialysis and peritoneal dialysis. No further dosage modification is required for patients on either hemodialysis or peritoneal dialysis.

The effect of hepatic failure

The liver is the major site for the metabolism of quinolones. At one end of the spectrum, ciprofloxacin pharmacokinetics is not significantly altered in cirrhotic patients and of the three metabolites only the formation of the oxo-metabolite was altered showing a 50% reduction; therefore, no dosage adjustment appears to be needed.

Ofloxacin pharmacokinetics is markedly influenced especially in alcoholic cirrhosis. Ofloxacin plasma concentrations are higher in cirrhotics and the $t_{\frac{1}{2}}$ is 1.5–2.0 times longer. One study also found the apparent volume of distribution to be only 67% of that found in healthy controls [26]. Lomefloxacin has a similar pharmacokinetic profile to ofloxacin

and is not affected in severe liver disease. The effect of impaired hepatic function on lomefloxacin pharmacokinetics was investigated in 12 patients with chronic hepatic cellular insufficiency due to cirrhosis [23]. There was no correlation between apparent non-renal clearance and hepatic insufficiency (Pugh's score), or apparent non-renal clearance and plasma bilirubin. Pefloxacin elimination is markedly delayed in cirrhotic patients due to a decrease in pefloxacin total clearance of more than 70%. The volume of distribution is also decreased. Dosage adjustment may be necessary with pefloxacin in cirrhotic patients [6].

The effect of age

Ofloxacin and ciprofloxacin have significantly different pharmacokinetics in the elderly compared with the young. In elderly patients, significantly higher C_{max} and AUC occur due to increased bioavailability, a reduced volume of distribution, and reduced renal clearance. The reduction in clearance is related to reduced renal function in the elderly patient. Dosage reduction may be required in elderly patients when the GFR is < 20–30 ml/min. As lomefloxacin is primarily eliminated by renal mechanisms, the elderly are likely to have decreased total clearance as the GFR declines with age [8]. The effect of age on lomefloxacin elimination was investigated in 16 elderly patients aged 60–75 years and compared to that in eight healthy volunteers aged 26–39 years [46]. There was no apparent age dependence in this relationship confirming that decreased plasma clearance in the elderly is a direct consequence of diminished renal function.

Conclusions

The fluoroquinolones have now been established as a major class of agents in the treatment of infections. Whilst there are differences in terms of in vitro activity (i.e. minimum inhibitory concentrations, MICs), there are also differences in their pharmacokinetic profiles and drug interactions. All these factors should be considered when deciding on the most appropriate fluoroquinolone to use in individual patients.

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Comparative study of the in vitro activity of lomefloxacin versus lomefloxacin combined with metronidazole versus lomefloxacin in combination with amoxicillin/clavulanic acid against *Chlamydia trachomatis*

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The role of Chlamydia trachomatis *in both acute and chronic salpingitis is well known but other bacterial species can act symbiotically with this organism to enhance pathogenicity. The advent of the fluoroquinolones – with their very broad spectrum of activity particularly on chlamydial species, gonococci and the Enterobacteriaceae – has raised the possibility that new antibiotic combinations may be used in the treatment of salpingitis. Since* Chlamydia trachomatis *is an intracellular pathogen, we devised a cell culture system to evaluate the efficacy (or any antagonistic effects) of lomefloxacin in combination with metronidazole and lomefloxacin in combination with amoxicillin/clavulanic acid. Our study showed that there appeared to be no inoculum effect. In addition, we found no in vitro antagonism between lomefloxacin and metronidazole or lomefloxacin and amoxicillin/clavulanic acid against* Chlamydia trachomatis. *These results justify the use of these combinations in vivo in patients infected with* Chlamydia trachomatis *infections.*

Key words: Lomefloxacin; Metronidazole; Amoxicillin/clavulanic acid; *Chlamydia trachomatis*

Introduction

The role of *Chlamydia trachomatis* in both acute and chronic salpingitis is well known. However, other bacterial species can act symbiotically with this organism to enhance pathogenicity. These accompanying symbiotic bacteria are essentially gonococci and members of the Enterobacteriaceae, especially *Escherichia coli* and anaerobes.

In order for an antimicrobial therapeutic strategy to have the best chance of success, the antibiotic must have a broad spectrum of activity against all these bacteria. However, appropriate antibiotic

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