Sparfloxacin : An Overview of Its Efficacy in ENT Infections

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INTRODUCTION

In recent years, the fluoroquinolones have become established as important antibacterial agents, characterised by rapid bactericidal activity against a broad spectrum of pathogens. Among the currently available agents, ciprofloxacin and ofloxacin have been extensively used to treat both upper and lower respiratory tract infections. However, with the widespread use of these agents, concerns have been expressed with regard to their activity against Gram-positive organism, especially *Streptococcus pneumoniae* (1).

With the rapid world-wide increase of penicillin-resistant pneumococci, alternative antibacterial agents are being sought. One strategy has been to seek new quinolone antibiotics with enhanced Gram-positive activity. Sparfloxacin is the first of these agents to have been developed clinically and is currently licensed in several countries (1).

Sparfloxacin is administered orally and penetrates well into various body fluids. It has a long elimination half-life allowing once daily administration, which enhances compliance and therefore overall efficacy. Because of these advantageous pharmacokinetic characteristics, coupled with a broad spectrum of antibacterial activity, sparfloxacin has been investigated in a variety of serious infections, including upper and lower respiratory tract infections, tuberculosis, urinary tract infections, sexually transmitted diseases, non-gonococcal urethritis and other serious infections.

This paper will concentrate on the efficacy of

Sparfloxacin in a variety of otorhinolaryngological ENT infections with particular emphasis on acute purulent sinusitis.

PHARMACOLOGICAL HIGHLIGHTS

Chemical Structure

Sparfloxacin is a difluorinated quinolone (see figure). The fluorine atom at position 8 increases absorption and plasma half-life, and the C-5 amino group confers enhanced in vitro activity against Gram-positive bacteria. The cyclopropyl group at position 1 and the fluorine atom at position 6 in the quinolone ring provides activity against Gram-negative bacteria, while association of the C-5 amino group and the C-7 dimethyl piperazine group to the molecule improves in vivo antibacterial activity, particularly against streptococcal infections (2).

The mechanism of action of Sparfloxacin involves the inhibition of DNA gyrase. Inhibition of this essential enzyme leads to interruption of normal DNA replication and, eventually, bacterial cell lysis (2).

Figure 1 : Structure of Sparfloxacin.

The fourth-step quinolone

Sparfloxacin represents the fourth step in the development of the quinolone antibacterial agents (table I). The antibacterial spectrum of sparfloxacin is wider than those of the third step quinolones, the later agents having limited activity against staphylococci, pneumococci, *Bacteroides fragilis*, and the genera chlamydia and mycoplasma (3).

The antibacterial spectrum of sparfloxacin is also wider than those of penicillins, cephalosporins, tetracycline and macrolides. Thus, sparfloxacin is considered to have the widest antibacterial spectrum among currently available agents.

Table I
History of quinolones

Step	Agent
First step (1962-1969)	Nalidixic acid Piromidic acid
Second step (1970-1977)	Cinoxacin Pipemidic acid
Third step (1978-1985)	Norfloxacin Ciprofloxacin Ofloxacin Pefloxacin Lomefloxacin
Fourth step (1986-present)	Sparfloxacin

SPECTRUM OF ANTIBACTERIAL ACTIVITY

Sparfloxacin is a broad-spectrum antibacterial agent. It is more active against Gram-positive, intracellular and anaerobic organisms than earlier fluoroquinolones and has good activity against a range of Gram-negative organisms. The activity of sparfloxacin against common upper respiratory tract pathogens is briefly discussed below :

i) Gram-positive organisms

a) *Streptococcus pneumoniae*

There has been a significant world-wide increase in the number of B-lactam and/or macrolide-resistant strains of *S. pneumoniae*.

In cases of high-level resistance to penicillin, treatment failures and recurrence of the infections have significant consequences for the patient. Sparfloxacin is active against pneumococci regardless of their resistance to penicillin or erythromycin and this represents an important clinical step forward in the treatment of both upper and lower respiratory tract infections in particular (4).

b) *Staphylococcus aureus*

The intrinsic activity of Sparfloxacin against *S. aureus* is about 10-fold higher than that of ciprofloxacin or ofloxacin with MIC 90 of Sparfloxacin being 0.125 mg/L (4).

ii) Gram-negative Bacterial

Sparfloxacin is very active in vitro against a wide range of Gram-negative bacteria, including *Haemophilus influenzae*, *Moraxella catarrhalis*, enterobacteriaceae and neisseria species (4). Sparfloxacin is also considerably more active than macrolides against common respiratory pathogens such as *H. influenzae* and *M. catarrhalis* (table II) (data on file).

Table II
Antibacterial activity of Sparfloxacin vs. macrolides
(MIC 90 values;mg/L)

Organism	Sparfloxacin	rixithromycin	Erythromycin
<i>S.pneumoniae</i>	<0.06-1.0	0.25	0.12-4.0
<i>H.influenzae</i>	0.008-0.06	8.7	4.3
<i>K.pneumoniae</i>	0.008-4.0	...	...
<i>M.catarrhalis</i>	<0.06	1.0	0.25
<i>M.pneumoniae</i>	0.063-0.25	0.03	0.004-0.03
<i>Legionella spp.</i>	0.06	0.5	0.0125-0.5

An ellipsis (...) indicates minimal activity

a) *Haemophilus influenzae*

Sparfloxacin is extremely active against *H. influezae*, regardless of whether the strain is B-lactam-susceptible or resistant, and is possibly more bactericidal than B-lactams against *H. influezae*. The activity of sparfloxacin against *H. influenzae* is twice

as high as that of ciprofloxacin or ofloxacin (4).

b) *Moraxella catarrhalis*

B-lactamase production is currently widespread in *M.catarrhalis* isolates, with more than 85% of strains resistant to ampicillin. Sparfloxacin is highly bactericidal against *M.catarrhalis*, being more active than Ciprofloxacin or ofloxacin against B-lactamase-positive clinical isolates (4).

iii) Atypical bacteria

Chlamydia pneumoniae is an important cause of community-acquired respiratory tract infections. The infection is rarely diagnosed and conventional B-lactam therapy is ineffective. Sparfloxacin has considerably greater activity than ofloxacin and ciprofloxacin against *C.pneumoniae* and is 5 to 6 times more active in vitro than erythromycin (4).

Pharmacokinetic profile (5, 6)

i) Absorption

- * Well absorbed after oral administration.
- * Steady-state plasma concentrations reached from the first day of administration, by use of a loading dose that is double the daily dose.
- * Absorption unaffected by food.

ii) Distribution

- * Widely distributed in the body.
- * Good penetration into the body tissues, including pulmonary tissues and fluids and sinus tissue.
- * Respiratory tract penetration superior to ciprofloxacin and lomefloxacin
- * In the nasal mucosa, sinus mucosa and tonsils, tissue concentrations are 5 times higher than plasma concentrations. In addition, according to Wise and Honeybourne, the mean sinus mucosa concentration for Sparfloxacin after a

single 400 mg dose of the drug was 9-fold greater than the mean plasma concentration of 0.81 mg/L.

- * Plasma protein binding = 45%.

iii) Metabolism

- * Metabolised by the liver to an inactive glucuronide conjugate.

iv) Elimination

- * Long elimination half-life, 18 to 20 hours allowing once-daily administration.
- * elimination is complete: two-thirds in the faeces and one-third in the urine.
- * Biliary excretion, mainly as glucuronide conjugate, accounts for 10 to 20% of the administered dose.
- * No modification of the pharmacokinetic parameters observed in elderly subjects.
- * The terminal plasma elimination half-life is 35 to 40 hours in subjects with severe renal insufficiency without cholestasis.

Therapeutic efficacy

Infections of the respiratory tract are responsible for major morbidity and account for most antibiotics prescribed within a community setting. The control of respiratory tract infections continues to represent a challenge both to the clinician and the researcher. The better respiratory tract penetration of Sparfloxacin, in conjunction with its superior activity against *S.pneumoniae* in particular suggest that sparfloxacin should be a suitable choice amongst the fluoroquinolones to treat a wide variety of infections of the respiratory tract. Sparfloxacin also achieves good concentrations in the sinus mucosa and has been shown to be effective clinically in the treatment of acute sinusitis and other otorhinolaryngological infection.

The two important clinical trials outlining the role of Sparfloxacin in various otorhinolaryngological infections are discussed below :

1) Japanese Collaborative Study Group of Sparfloxacin in Otorhinolaryngology (7).

An open multicentric clinical study to evaluate the efficacy and safety of orally administered sparfloxacin in the field of otorhinolaryngology was performed by the study Group in Japan 77 male and 114 female patients aged 16 to 95 (mean 47.3) years with clear signs and symptoms of otitis media (n=101), otitis externa (n=14) and sinusitis (n=76) were included in the study. A total of 181 strains comprising 128 strains of Gram-positive bacteria (including 64 strains of methicillin-sensitive *S.aureus* and 5 strains of methicillin-resistant *S.aureus*), 50 strains of Gram-negative bacteria (including 12 strains of *Pseudomonas aeruginosa*) and anaerobic bacteria (3 strains) were isolated before treatment. Sparfloxacin was administered at a daily dose of 200 mg or 300 mg. once or twice daily, for 3 to 14 days. Clinical efficacy was evaluated on the basis of improvement in symptoms, such as the amount of exudate and sensation of blockage. In sinusitis, clinical efficacy was also evaluated by the improvement in X-ray findings. As shown in table 3, clinical efficacy rates for sparfloxacin in otitis media, otitis externa and sinusitis were 72.3%, 100% and 82.9%, respectively. The efficacy rate in acute cases was higher than that in chronic cases. Bacteriological effect was evaluated in 181 strains, and the total eradication rate was 89.0%. The eradication rates achieved against Gram-positive and Gram-negative bacteria were 89.8% and 86.0%, respectively.

The results suggested that sparfloxacin possesses a broad antibacterial spectrum against both Gram-positive and Gram-negative bacteria. Also, it was noteworthy that sparfloxacin showed a high eradication rate against methicillin resistant *S.aureus* (80.0%), even though no more than 5 strains ere examined.

On the basis of these results, the Study Group concluded that Sparfloxacin is a useful antimicrobial agent in the field of otorhinolaryngology.

2) European multicentre trial of Sparfloxacin in acute purulent sinusitis (8).

In a randomised double-blind, comparative multicentre trial conducted by the Sinusitis Study Group in Europe, 382 patients with a diagnosis of acute purulent sinusitis (<3 weeks duration) were enrolled for the study. The diagnosis was based on the following criteria : pus on the middle meatus and/or purulent rhinorrhoea and pain or tenderness over the affected sinuses. A sample of sinus discharge was taken by aspirate from the middle meatus for microbiological culture and sensitivity test. Administration of other antibacterial agents within 48 h before inclusion in the study, systemic or local corticosteroid therapy within 7 days of inclusion and the use of non-steroidal anti-inflammatory drugs was not allowed. Patients with a history of hypersensitivity

Table 3
Clinical efficacy of sparfloxacin in otorhinolaryngological infections

Diagnosis	No.of Patients	Excellent	Efficacy good	fair	poor	Efficacy Rate (%)
1. Otitis media						
Acute	30	15	10	3	2	83.3
Chronic	71	23	25	12	11	67.6
Subtotal	101	38	35	15	13	72.3
2. Otitis-External	14	12	2	—	—	100
3. Sinusitis						
Acute	41	22	15	3	1	90.2
Chronic	35	10	16	7	2	74.3
Subtotal	76	32	31	10	3	82.9
4. Total	191	82	68	25	16	78.5

to quinolones of B-lactams and women who were pregnant or breastfeeding were excluded from the study. Patients were assigned randomly to receive either sparfloxacin (400 mg on day 1, 200 mg on days 2-5, and placebo on days 6-8) (n=193) or cefuroxime axetil (250 mg twice daily on days 1 to 8) (n=189). Patients were classified as success or failure according to clinical symptoms plus bacteriological and radiological data at the end of treatment and at a follow-up visit. In analysis of the intent-to-treat (n=374) and evaluable populations (n=304), the 5 day course of sparfloxacin was at least as effective and well tolerated as the 8 day course of cefuroxime axetil. The success rates at the end of treatment in the evaluable population were 82.6% and 83.2% in the sparfloxacin and cefuroxime axetil groups, respectively. The pathogens isolated most frequently were *Haemophilus influenzae* (33%) and *Streptococcus pneumoniae* (28%). Response rates according to the bacterial aetiology of the acute sinusitis were similar in the two treatment groups (Table IV). Both drugs were well tolerated.

Table IV

Overall efficacy according to the bacterial aetiology in the evaluable population at follow-up.

	Sparfloxacin	Cefuroxime axetil
<i>H.influenzae</i>	43/51 (84.3%)	32/38 (84.2%)
<i>S.pneumoniae</i>	34/38 (89.5%)	36/39 (92.3%)
<i>M.catarrhalis</i>	16/17 (94%)	11/13 (85%)
<i>S.aureus</i>	14/14 (100%)	14/18 (78%)
Enterobacteriaceae	13/14 (93%)	14/14 (100%)
<i>P.aeruginosa</i>	1/2	2/3
B-haemolytic streptococci	1/3	—

The commonest adverse events were gastrointestinal and were reported in 2.6% and 3.8% of sparfloxacin and cefuroxime axetil-treated patients, respectively.

In conclusion, this study demonstrated in a well-defined population of out-patients suffering with acute purulent sinusitis that sparfloxacin 200 mg once daily for 5 days could be a suitable

empirical antibiotic treatment. The Study Group further opined that Sparfloxacin may be a particularly appropriate choice in countries where there is a high incidence of B-lactamase producing strains of *H.influenzae* or *S.pneumoniae* that are not fully susceptible to penicillin.

Tolerability (9)

Safety data is available from 529 volunteers or patients included in phase I trials of Sparfloxacin and 4092 patients included in phase III trials during the European development of the drug. Various controlled trials have enabled direct comparison of tolerability data for sparfloxacin and other antibacterial agents such as amoxycillin, amoxycillin/clavulanic acid, erythromycin, cefuroxime axetil, ciprofloxacin and doxycycline.

The incidence of adverse events with sparfloxacin was low and compared favourably with the incidents recorded for other antibacterial agents. Sparfloxacin was also well tolerated in populations considered to be 'at-risk' such as diabetics, patients aged >70 years and those with hepatic or moderate renal dysfunction. Events affecting the gastrointestinal system were reported most frequently, mainly diarrhoea, nausea and vomiting.

A slight prolongation (<3%) of the QT interval, less than that observed with erythromycin, has been reported with Sparfloxacin, but appears to be without any clinical cardiovascular consequences. Nevertheless, it is currently recommended that patients treated with Sparfloxacin should not receive concomitant administration of other drugs known to prolong the QT interval. All fluoroquinolones currently marketed have the potential to induce photosensitivity in nearly 2% of patients. The incidence of photosensitivity in patients treated with Sparfloxacin was similar (1.9%).

Drug Interactions (10)

Antacids are known to significantly decrease the bio-availability of the fluoroquinolones, including

sparfloxacin. In contrast, sparfloxacin does not affect the metabolism of theophylline as do some other quinolones and macrolides, and thus sparfloxacin can be used safely in patients who required theophylline as part of their management.

If possible, patients should avoid taking antacids containing aluminium while being treated with Sparfloxacin. Since there is convincing evidence that drugs such as sucralfate and those containing metallic ions may inhibit the absorption of quinolones in general, sparfloxacin should be administered with caution to patients receiving those agents. Administering sparfloxacin 2 hours before any of these agents may minimise any effects on the absorption of sparfloxacin. Cimetidine, however, has no effect on sparfloxacin's bioavailability. Sparfloxacin may increase plasma digoxin levels and thus patients receiving both drugs should be closely monitored.

Precautions (11)

Contraindications

Sparfloxacin is contraindicated in patients who are hypersensitive to fluoroquinolones. It should be prescribed to women who are pregnant or breast-feeding or to children and adolescents who are still growing.

Special precautions

It is recommended that the use of drugs known to prolong the QT interval be avoided in patients receiving sparfloxacin. If concurrent treatment is necessary, patients should be closely monitored.

Sparfloxacin can cause photosensitivity and undue exposure to sunlight or ultraviolet radiation should be avoided during treatment and for 3 days afterwards.

For patients with renal dysfunction where creatinine clearance is <30 ml/min, the following is recommended : either a dosage interval twice the usual interval, or a decrease in the daily dosage by half, i.e. sparfloxacin 400 mg loading

dose followed by either 200mg every other day or 100 mg daily. There are no special dosage recommendations for patients with hepatic dysfunction.

Dosage and administration in ENT infections

Loading dose of 400 mg followed by 200 mg daily for a total treatment duration of 5 days.

CONCLUSIONS

Fluoroquinolone antibacterial agents have till date not been accepted as a primary line of empirical monotherapy of both upper and lower respiratory tract infections mainly because of their insufficient activity against *S. pneumoniae*. Selecting empirical treatment for these infections has become even more difficult for the physician, in view of the increasing incidence of *S.pneumoniae* strains resistant to various antibacterial agents.

Sparfloxacin, with a broad spectrum of activity and excellent pharmacokinetic properties, offers a valuable option in this situation. It has an excellent *in vivo* and *in vitro* activity against *S.pneumoniae*, regardless of whether the strain is resistant to penicillin, tetracycline or erythromycin. *H.influenzae*, another common pathogen in respiratory tract infections, is also highly susceptible to sparfloxacin. In addition, sparfloxacin is active against *M.pneumoniae*, *C.pneumoniae*, and *L.pneumophila*, organisms that are implicated in 'atypical' community – acquired pneumonia and in upper respiratory tract infections. Sparfloxacin has been found to be extremely useful in a variety of otorhinolaryngological infections. The success rate with sparfloxacin in acute sinusitis is not only comparable to therapy with cefuroxime axetil, but use of the fluoroquinolone enables the duration of treatment of this infection to be shortened from 8 to 5 days.

The efficacy of an antibacterial agent is dependent not only on its activity against the infecting organism and pharmacokinetic profile, but also on the patients' compliance with therapy.

Because it is administered once daily, sparfloxacin maximises compliance, particularly for elderly patients or patients receiving multi-drug regimens, and its good tolerability means few patients discontinue treatment because of adverse events. Unlike certain macrolides and various quinolones, sparfloxacin does not affect plasma theophylline levels and patients receiving both drugs do not require additional

monitoring.

Sparfloxacin, with its once-daily dosage and broad spectrum of activity thus provides the medical fraternity with an important new option for first-line empirical treatment of both upper and lower respiratory tract infections including community-acquired pneumonia, exacerbation of COPD and acute sinusitis.

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