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Susceptibility of bacterial isolates from AIDS patients to six fluoroquinolones

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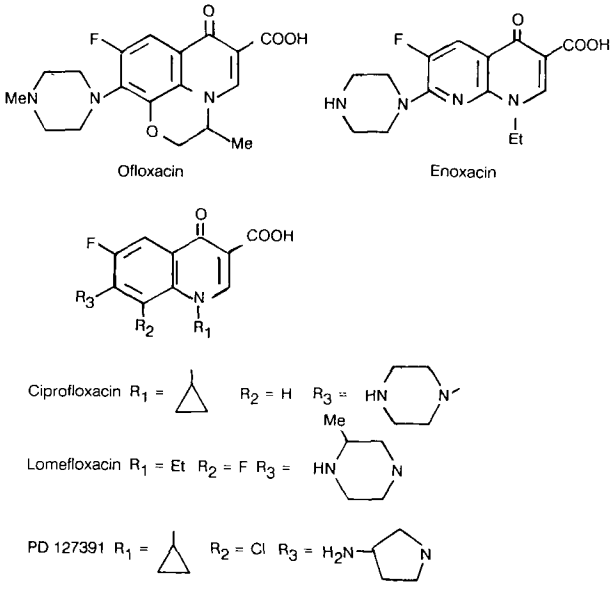
Abstract—The susceptibilities to ciprofloxacin, DR-3355 (*S*-(−)-ofloxacin), enoxacin, lomefloxacin, ofloxacin and PD127,391 of 69 significant bacterial isolates from HIV-positive patients at the City Hospital, Edinburgh have been determined. With the exception of the enterococci, most of the strains tested (including staphylococci, *Escherichia coli* and *Pseudomonas aeruginosa*) were susceptible to the fluoroquinolones. Ciprofloxacin was the most active of the clinically available drugs followed by ofloxacin, lomefloxacin and enoxacin. PD127,391 and DR-3355, the new fluoroquinolones tested, were at least as active as ciprofloxacin. Hence bacterial infections in AIDS patients should respond to fluoroquinolone therapy.

The fluoroquinolones are relatively non-toxic, broad spectrum, bactericidal antimicrobials for which plasmid-mediated resistance has yet to be identified (Andriole 1988; Smith & Lewin 1988; Lewin et al 1990). These characteristics render the fluoroquinolones suitable candidates for the treatment of the opportunistic infections that are liable to occur in patients suffering from acquired immunodeficiency syndrome (AIDS) (Young 1987; Sande 1989). Indeed, the fluoroquinolones have already been used to treat infections in AIDS patients, particularly salmonella bacteraemias (Bogner & Goebel 1986; Rolston et al 1988; Jacobsen et al 1989). It is tempting to assume that organisms in AIDS patients will not differ from similar organisms isolated from other seriously ill patients and thus will be sensitive to the fluoroquinolones. However, little information actually exists on the susceptibility to the fluoroquinolones of bacterial pathogens isolated from AIDS patients. We have therefore examined the sensitivity of 69 significant bacterial isolates from human immunodeficiency virus (HIV) positive patients at the City Hospital, Edinburgh, to six fluoroquinolones. Four of the fluoroquinolones chosen for the investigation, ciprofloxacin, enoxacin, lomefloxacin and ofloxacin, are available clinically. Two drugs which are not yet available for clinical use were also included in this study. PD127,391, an enhanced spectrum quinolone, that displays in-vitro activity against a wide range of species (King et al 1988; Wise et al 1988) and DR-3355, the *S*-(−)-isomer of ofloxacin, which, in-vitro, is twice as active as ofloxacin (Une et al 1988; Lewin & Amyes 1989).



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Materials and methods

Antimicrobials. Ciprofloxacin (Bayer UK), DR-3355 (*S*-(−)-ofloxacin) (Daiichi Pharmaceutical, Japan) and PD127,391 (Parke-Davis, UK) were dissolved in sterile distilled water. Enoxacin (Parke-Davis, UK), lomefloxacin (Searle, UK) and ofloxacin (Hoechst, UK) were dissolved in 0·5 M NaOH (0·02 mL per mg) before being made up to the appropriate concentration in sterile distilled water.

Bacterial strains. The 69 significant bacteria were isolated between February 1989 and January 1990 from HIV positive patients at the City Hospital, Edinburgh.

Minimum inhibitory concentrations (MIC). MICs were determined on Diagnostic Sensitivity Test Agar (Oxoid, UK) employing an arithmetic dilution scheme described by Smith (1984). An inoculum of 10^4 colony forming units (cfu) per spot was placed on the plates using a multipoint inoculator (Denley UK). The MIC was taken as the lowest concentration which inhibited visible growth after overnight incubation of the plates at 37°C.

Results

The comparative in-vitro activities of ciprofloxacin, DR-3355, enoxacin, lomefloxacin, ofloxacin and PD127,391 are shown in Table 1. Most of the 29 Gram-negative bacterial isolates tested were susceptible to all six drugs, most of the bacteria having MICs < 1 mg L^{-1}. Differences were observed in the activity of the fluoroquinolones against the 40 staphylococci and enterococci tested. PD127,391 was the only compound active against the six enterococci tested (MIC50 0·5 mg L^{-1}, Table 1). Most of the 34 staphylococcal isolates tested were susceptible to ciprofloxacin, DR-3355, lomefloxacin, ofloxacin and PD127,391 (MIC90 $\leq 0{\cdot}4$ mg L^{-1}) but only marginally susceptible to enoxacin (MIC50 and MIC90 1·5 mg L^{-1}).

Ciprofloxacin was the most active of the four clinically available fluoroquinolones tested against these isolates followed by ofloxacin, lomefloxacin and enoxacin. Both of the new fluoroquinolones tested, DR-3355 and PD127,391, were highly active against these strains. The activity of DR-3355 was similar to that of ciprofloxacin and twice as active as ofloxacin. PD127,391 was at least as active as ciprofloxacin against the Gram-negative bacteria. Furthermore, PD127,391 was 10-fold more active than either ciprofloxacin or DR-3355 against the Gram-positive isolates. For example against the staphylococci the MIC90 was 0·04 mg L^{-1} compared with 0·4 mg L^{-1} for ciprofloxacin and 0·3 mg L^{-1} for DR-3355.

Table 1. MICs (mg L^{-1}) of strains isolated from HIV patients.

Species	Range	MIC50	MIC90
Enterobacteriaceae[a] (20)			
Ciprofloxacin	<0·0075–1	0·015	0·075
Ofloxacin	0·04–0·75	0·075	0·3
DR-3355	0·02–0·5	0·04	0·2
Enoxacin	0·1–1·5	0·15	0.75
Lomefloxacin	0·075–1·5	0·1	0·4
PD127,391	<0·0075–0·02	<0·0075	0·02
Ps. aeruginosa (9)			
Ciprofloxacin	0·04–0·3	0·15	—
Ofloxacin	0·2–4	0·5	—
DR-3355	0·1–2	0·3	—
Enoxacin	0·3–3	0·75	—
Lomefloxacin	0·3–5	0·75	—
PD127,391	0·02–0·5	0·075	—
Staphylococci[b] (34)			
Ciprofoxacin	0·3–5	0·3	0·4
Ofloxacin	0·2–3	0·3	0·4
DR-3355	0·1–1·5	0·2	0·3
Enoxacin	0·75–7·5	1·5	1·5
Lomefloxacin	0·5–5	0·3	0·4
PD127,391	0·015–0·5	0·03	0·04
Enterococci[c] (6)			
Ciprofloxacin	1·5–7·5	3	—
Ofloxacin	3–5	5	—
DR-3355	1·5–3	1·5	—
Enoxacin	7·5–15	7·5	—
Lomefloxacin	5–7·5	5	—
PD127,391	0·5–1	0·5	—

[a] Includes 17 *E. coli* plus one strain each of *Enterobacter*, *Klebsiella*, and *Hafnia*.
[b] Includes 29 *S. aureus* and 5 coagulase negative staphylococci.
[c] Includes 4 *E. faecalis* plus one strain each of *E. faecium* and *E. avium*.

Discussion

The susceptibility pattern of the isolates from HIV positive patients at the City Hospital, Edinburgh appeared to be similar to that reported for bacterial pathogens in the general population in the UK (Lovering et al 1988). Most of the 29 Gram-negative bacterial isolates were sensitive to the six fluoroquinolones tested. The staphylococci tested were, at best, marginally susceptible to enoxacin but sensitive to the other five drugs. PD127,391 was the only compound active against the enterococci isolated from the HIV positive patients. The lack of susceptibility of the enterococci is not particularly surprising as other surveys have reported marginal sensitivity of the enterococci to the fluoroquinolones (Phillips et al 1988; Paton et al 1989). PD127,391 was 10-fold more active than the other compounds against the staphylococci. This increase in activity against Gram-positive bacteria compared with the other quinolones may be highly relevant as these organisms formed most of the clinically significant isolates in the HIV positive patients and staphylococci appear to be able to develop resistance to the 4-quinolones in current use relatively easily (Lewin et al 1990). In conclusion these data suggest that pathogens isolated from HIV-positive patients do not differ from pathogens in other seriously ill patients in their sensitivity to the fluoroquinolones. Thus, this class of antimicrobial may play a useful role in the treatment of bacterial infections that are likely to occur in such patients.

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References

Andriole, V. T. (1988) Clinical overview of the newer 4-quinolone antibacterial agents. In: Andriole, V.T. (ed.) The Quinolones. Academic Press London, pp 155–200

Bogner, T., Goebel, F. D. (1986) Recurrent Salmonella bacteraemia in a patient with acquired immunodeficiency syndrome. Aids Forschung 1: 669–671

Jacobsen, M. A., Hahn, S. M., Geberding, J. L., Lee, B., Sande, M. A. (1989) Ciprofloxacin for Salmonella bacteraemia in acquired immunodeficiency syndrome (AIDS). Anns. Int. Med. 110: 1027–1029

King, A., Boothman, C., Phillips, I. (1988) The in-vitro activity of PD127,391, a new quinolone. J. Antimicrob. Chemother. 22: 135–141

Lewin, C. S., Amyes, S. G. B. (1989) Bactericidal activity of DR-3355, an optically active isomer of ofloxacin. J. Med. Microbiol. 30: 227–231

Lewin, C. S., Allen, R. A., Amyes, S. G. B. (1990) Potential mechanisms of resistance to the modern fluorinated 4-quinolones. Ibid. 31: 153–162

Lovering, A. M., Bywater, M. J., Holt, H. A., Champion, H. M., Reeves, D. S. (1988) Resistance of bacterial pathogens to four aminoglycosides and six other antibacterials and prevalence of aminoglycoside modifying enzymes in 20 UK centres. J. Antimicrob. Chemother. 22: 823–840

Paton, R., Lewin, C. S., Hood, J., Amyes S. G. B. (1989) Sensitivity testing of enterococci to ciprofloxacin. Ibid. 24: 265–266

Phillips, I., King, A., Shannon, K. (1988) In vitro properties of the quinolones. In: Andriole, V.T. (ed.) The Quinolones. Academic Press London, pp 83–117

Rolston, K. V., Rodriguez, S., Mansell, P. W. A. (1988) Antimicrobial therapy for Salmonella infections in the acquired immunodeficiency syndrome (AIDS). Anns. Int. Med. 108: 309

Sande, M. (1989) Antimicrobial therapy in Aids patients—an overview. J. Antimicrob. Chemother. 23 (Suppl. A): 63–65

Smith, J. T. (1984) Mutational resistance to the 4-quinolone antibacterial agents. Eur. J. Clin. Microbiol. 3: 347–350

Smith, J. T., Lewin, C. S. (1988) Chemistry and mechanisms of action of the quinolone antibacterials. In: Andriole, V.T. (ed.) The Quinolones. Academic Press, London, pp 23–82

Une, T., Fujimoto, T., Sato, K., Osada, Y. (1988) In-vitro activity of DR-3355, an optically active ofloxacin. Antimicrob. Agents Chemother. 32: 1336–1340

Wise, R., Ashby, J. P., Andrews, J. M. (1988) In-vitro activity of PD127,391, an enhanced spectrum quinolone. Ibid. 32: 1251–1256

Young, L. S. (1987) Infection today: treatable aspects of infections due to acquired immunodeficiency virus. Lancet ii: 1503–1506