Ciprofloxacin in experimental *Pseudomonas aeruginosa* meningitis in rabbits

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The potential of ciprofloxacin for the therapy of *Pseudomonas aeruginosa* meningitis was evaluated in an animal model by determining the penetration of the drug into CSF, its concentration-dependent killing characteristics *in vivo*, and its relative efficacy compared with ceftazidime and tobramycin.

Meningitis was produced in 40 rabbits by intracisternal injection of 3×10^7 organisms. The drugs were administered intravenously over seven hours, and simultaneous serum and CSF samples were taken at 0, 1, 3, 5, and 7 h for determination of drug concentration and CSF bacterial counts.

The percentage penetration of ciprofloxacin ($18\cdot4 \pm 12\cdot3$; mean $\pm$ standard deviation) in infected rabbits was substantially increased over that found in uninfected rabbits ($4\cdot1 \pm 1\cdot3$). The rate of bacterial killing for animals treated with ceftazidime (100 mg/kg/h) and high doses of tobramycin (2·5 mg/kg/h) was $-0\cdot51 \pm 0\cdot13$ ($\log_{10}$ cfu/ml/h). This was similar to the rate of killing ($-0\cdot48 \pm 0\cdot2$) found when ciprofloxacin was infused at 5 mg/kg/h, a dose that produced a mean serum level of $6\cdot7 \pm 4\cdot6$ mg/l, which corresponds to concentrations achievable in humans. As dosages were increased (15 and 30 mg/kg/h), the rate of bacterial killing also increased ($-0\cdot70 \pm 0\cdot1$ and $-0\cdot89 \pm 0\cdot4$ respectively; $r = 0\cdot7407$; $P < 0\cdot01$). The drug shows promise in the treatment of pseudomonas meningitis.

Introduction

Pseudomonas aeruginosa meningitis is an uncommon (McGee & Kaiser, 1985) yet important clinical problem because of its resistance to antimicrobial therapy. Forty per cent or more of patients die and over 60% of the survivors develop neurological complications (Mangi, Quintiliani & Andriole, 1975). This morbidity and mortality can be attributed in part to the fact that the patients at greatest risk are often debilitated and recovering from a head injury or neurosurgery.

Drugs commonly used in the treatment of Gram-negative bacillary meningitis are not effective against *Pseudomonas* spp. Broad-spectrum penicillins or third-generation cephalosporins that have anti-pseudomonal activity are effective in many infections caused by *Pseudomonas* spp. especially when used in combination with an aminoglycoside (McGee & Kaiser, 1985), but this treatment may not be successful in meningitis. Success may be increased if the aminoglycoside is administered by the intralumbar or intraventricular route (Mangi *et al.*, 1975; McGee & Kaiser, 1985). Because of the many inadequacies in the present therapeutic approach to

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pseudomonas meningitis, there is a need for a constant search for new anti-pseudomonal drugs that penetrate well into the CSF (Scheld, Kelly & Sande, 1980) and exhibit rapid bactericidal activity (Scheld & Sande, 1983).

Ciprofloxacin has an extended spectrum of activity which includes *P. aeruginosa* (Fass, 1983; Wise, Andrews & Edwards, 1983; Chin & Neu, 1984). We evaluated the potential of ciprofloxacin therapy for *P. aeruginosa* meningitis in an animal model (Dacey & Sande, 1974) by determining the penetration of the drug into CSF; its concentration-dependent killing characteristics *in vivo* and its relative efficacy compared with ceftazidime and tobramycin.

Materials and methods

Meningitis was established as previously described (Taeuber *et al.*, 1985) except that the infecting strain of *P. aeruginosa* (CSF isolate) was administered in 0·2 ml of 0·9% saline at a final concentration of $1-2 \times 10^8$ cfu/ml. Sixteen hours later therapy with either ciprofloxacin or ceftazidime/tobramycin was begun. Ciprofloxacin, in doses ranging from 1 to 30 mg/kg/h, was administered as a constant intravenous infusion for seven hours. Ceftazidime and tobramycin were infused intravenously at doses of 25 and 2·5 mg/kg/h, respectively. The tobramycin concentrations achieved in the CSF after this high intravenous dose were comparable with those found in humans after an intrathecal administration of the drug. Simultaneous blood and CSF samples were obtained at 0, 1, 3, 5, and 7 h for estimation of drug concentration and CSF bacterial counts.

The concentrations of ciprofloxacin in CSF and serum of uninfected rabbits were also determined, with doses of either 5 or 15 mg/kg/h. Simultaneous blood and CSF samples were obtained in the same manner as in the animals with an established infection. Serum and CSF were stored at $-70°C$ until drug assays were performed.

For each rabbit, the percentage penetration of drug into the CSF was calculated as:

$$(\text{CSF concentration/serum concentration}) \times 100.$$

The rate of bacterial killing was defined as change in bacterial titre ($\log_{10}$ cfu/ml)/h. Least squares regression analysis was used to analyse the correlation between CSF concentrations and the rate of bacterial killing.

In-vitro MICs and MBCs were determined by standard broth dilution methods in Mueller–Hinton broth (MHB) supplemented with Mg^{++} and Ca^{++} (Jones *et al.*, 1985). In-vitro time kill curves in MHB and in rabbit CSF were performed as we have reported previously (Shibl, Hackbarth & Sande, 1986). The detection of ciprofloxacin and ceftazidime in serum and CSF samples was by an agar well diffusion bioassay (Anhalt, 1985), with *Escherichia coli* ATCC 10536 as the test strain. For the tobramycin assay, *Staphylococcus epidermidis* ATCC 27626 was the test strain, and Broad-Spectrum Cephalosporinase (Oxoid), which inactivates ceftazidime, was added directly to the agar. To inactivate the aminoglycoside, 0·02 ml of 1·0 N HCl was added to 0·2 ml of each of the samples, thus lowering the pH to 5·0.

Results

The geometric means of the MIC and MBC values (mg/l) for the test strain were as follows: ciprofloxacin, 1/1; ceftazidime, 3·5/57; tobramycin, 0·8/2·6. The combination of ceftazidime and tobramycin is synergistic against this strain (Rusnak *et al.*, 1984).

Table I. Treatment of rabbits with pseudomonas meningitis: dosage, serum and CSF concentrations, % penetration and rate of killing

Dosage (mg/kg/h)	No. of rabbits	Mean concentration ±S.D. (mg/l)		Mean % penetration ±S.D.	Mean killing rate±S.D. ($\log_{10}$ cfu/ml/h)
		serum	CSF		
Ciprofloxacin					
1·0	4	1·1±0·5	0·1±0·1	10·8±7·5	−0·14±0·1
2·5	3	2·0±0·7	0·6±0·3	39·4±10·7	−0·16±0·1
5·0	7	6·7±4·6	0·8±0·2	17·3±12·6	−0·48±0·2
15·0	6	15·0±4·5	3·3±1·7	22·9±9·3	−0·70±0·1
30·0	7	48·2±15·3	5·1±2·2	10·9±3·7	−0·89±0·4
Ceftazidime/ tobramycin					
25·0	3	109·0±11·3	24·8±3·0	22·9±0·1	−0·51±0·1
2·5		9·9±4·0	3·1±1·2	32·9±2·1	
Untreated controls					
	9	—	—	—	+0·14±0·1

The percentage penetration of ciprofloxacin into the CSF of normal rabbits was 4·08±1·27% (mean±standard deviation), compared with 18·4±12·3% in infected rabbits (Table I).

At doses of 1·0 and 2·5 mg/kg/h, the rate of killing of *P. aeruginosa* for ciprofloxacin was less than that for the ceftazidime/tobramycin combination. At 5·0 mg/kg/h, a dose that approximated maximum serum levels that are achievable in humans, ciprofloxacin and the combination were equally effective in reducing bacterial titres. The rate of killing increased as the CSF concentration of ciprofloxacin increased (Figure 1). There
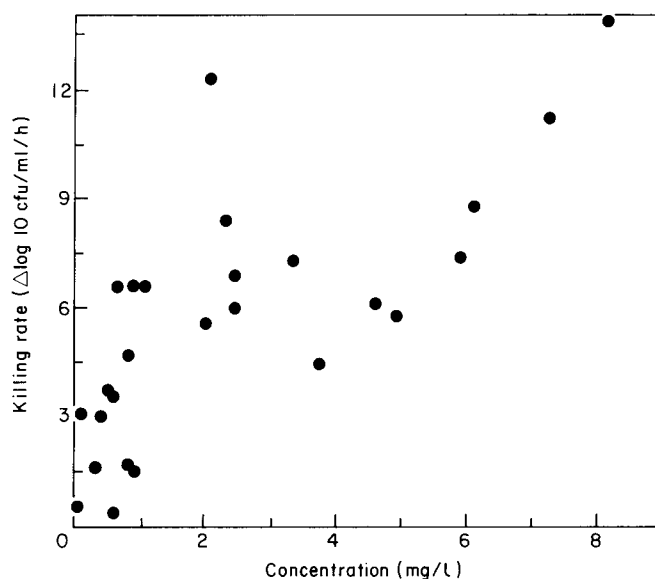
Figure 1. Correlation between CSF concentration of ciprofloxacin (mg/l) and bacterial killing rate ($\log_{10}$ cfu/ml/h) $r = 0.7407$; $P < 0.01$.
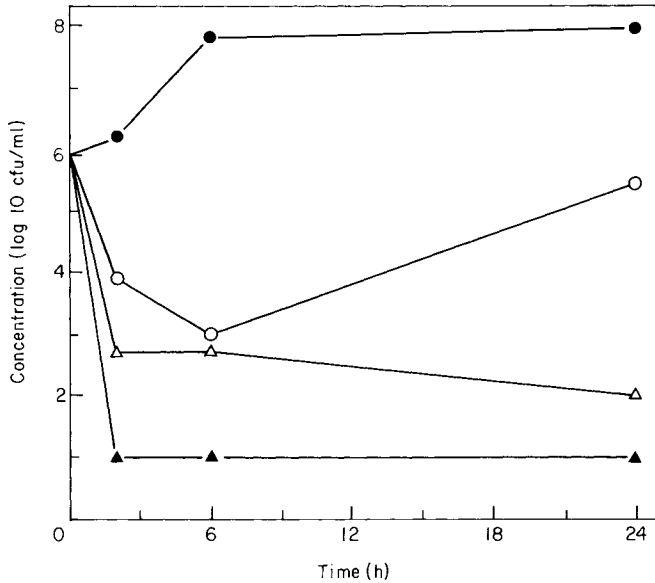
Figure 2. Dose dependent killing by ciprofloxacin: *in vitro* in CSF. ●, Control; ○, 1 mg/l ciprofloxacin; △, 5 mg/l ciprofloxacin; ▲, 10 mg/l ciprofloxacin.

was a good correlation between the CSF concentration and the rate at which the bacteria were killed ($r = 0.74$; $P < 0.01$). In the nine rabbits that were infected and left untreated, the bacteria in their CSF continued to grow at a rate of $0.14 \pm 0.05 \log_{10}$ cfu/ml/h.

There was a very rapid killing of the organisms by ciprofloxacin *in vitro* (Figure 2): both in CSF and in Mueller–Hinton broth, bacterial titres dropped 2–3 logs in the first 2 h.

Discussion

With currently available drugs, including the newer third-generation cephalosporins, *P. aeruginosa* meningitis cannot be consistently treated successfully with a single agent (Neu, 1985). However, ciprofloxacin, at a dose of 5 mg/kg was as effective for this experimental infection as the combination of ceftazidime and tobramycin—where the CSF concentrations of tobramycin were comparable with those achieved in humans after intrathecal administration of tobramycin.

In-vivo and in-vitro results demonstrated that the rate at which ciprofloxacin kills susceptible bacteria is directly dependent upon the drug concentration. This is similar to the concentration-dependent killing by aminoglycosides (Kapusnik & Sande, 1986). We have previously also demonstrated a similar effect *in vivo* with β-lactam antibiotics, where we obtained maximal killing when CSF drug concentrations reached 10–30 times the MBC for the infecting organism (Taeuber *et al.*, 1984).

Although no attempt was made to inactivate ciprofloxacin, the rapid killing we observed *in vivo* is probably not due to drug carry-over, which occurs when concentrations are greater than 30 times the MBC of the organism (Chalkley & Koornhof, 1985). These authors, too, found rapid killing of both stationary and log phase pseudomonas by ciprofloxacin.

Because of the remarkable susceptibility of *P. aeruginosa* to ciprofloxacin, and its favourable pharmacological characteristics (penetration into the CSF) this quinolone might be a useful new agent for the treatment of pseudomonas meningitis in humans.

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