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Parenteral Sparfloxacin Compared with Ceftriaxone in Treatment of Experimental Endocarditis Due to Penicillin-Susceptible and -Resistant Streptococci

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A new, investigational, parenteral form of sparfloxacin was compared with ceftriaxone in the treatment of experimental endocarditis caused by either of three penicillin-susceptible streptococci or one penicillin-resistant streptococcus. Both drugs have prolonged half-lives in serum, allowing single daily administration to humans. Sparfloxacin had relatively low MICs (0.25 to 0.5 mg/liter) for all four organisms and was also greater than or equal to eight times more effective than the other quinolones against 21 additional streptococcal isolates recovered from patients with bacteremia. Ceftriaxone MICs were 0.032 to 0.064 mg/liter for the penicillin-susceptible strains and 2 mg/liter for the resistant isolate. Both antibiotics resulted in moderate bacterial killing in vitro. Rats with catheter-induced aortic vegetations were inoculated with 10^7 CFU of the test organisms. Antibiotic treatment was started 48 h later and lasted either 3 or 5 days. The drugs were injected at doses which mimicked the kinetics in human serum produced by one intravenous injection of 400 mg of sparfloxacin (i.e., the daily dose expected to be given to human adults) and 2 g of ceftriaxone. Both antibiotics significantly decreased the bacterial densities in the vegetations. However, sparfloxacin was slower than ceftriaxone in its ability to eradicate valvular infection caused by penicillin-susceptible bacteria. While this difference was quite marked after 3 days of therapy, it tended to vanish when treatment was prolonged to 5 days. In contrast, sparfloxacin was very effective against the penicillin-resistant isolate, an organism against which ceftriaxone therapy failed in vivo. No sparfloxacin-resistant mutant was selected during therapy. Thus, in the present experimental setting, this new, investigational, parenteral form of sparfloxacin was effective against severe infections caused by both penicillin-susceptible and penicillin-resistant streptococci.

Streptococci are the most frequent causative agents of native-valve endocarditis (19). Classical treatment of such infection advocates several weeks of treatment with multiple daily injections of penicillin alone or in combination with aminoglycosides (2). Recently, a simplified therapeutic schedule consisting of single daily injections of ceftriaxone (a broad-spectrum cephalosporin which has a prolonged half-life in serum) (17) has been shown to cure successfully penicillin-susceptible streptococcal endocarditis in humans (10, 21). In addition, recent experiments also showed that single daily injections of ceftriaxone combined with netilmicin could cure endocarditis caused by penicillin-resistant streptococci in animals (4). Thus, simplified therapeutic schemes involving only one injection of antibiotics may become available for the treatment of both penicillin-susceptible and -resistant streptococcal endocarditis.

However, ceftriaxone therapy may present limitations in the numerous patients who are allergic to β-lactam antibiotics. In such patients, streptococcal endocarditis is usually treated with vancomycin (2), which also requires multiple daily injections and carries an additional risk of nephrotoxicity when it is used in combination with aminoglycosides (15). Therefore, there is a rationale to seek new compounds which would combine the advantages of (i) having a prolonged half-life in the serum of humans, (ii) producing no cross-allergy with β-lactam antibiotics, (iii) having a low level of toxicity, and (iv) being effective against endocarditis caused by streptococci and other organisms.

In the experiments described below, we tested the efficacy of a new, investigational, parenteral form of sparfloxacin in the treatment of experimental streptococcal endocarditis. Sparfloxacin belongs to a new group of quinolones: it has a prolonged half-life in serum and increased activity against gram-positive cocci compared with the half-lives and activities of the previous molecules from this group of antibiotics.

MATERIALS AND METHODS

Microorganisms. Four clinical isolates of streptococci recovered from patients with endocarditis were used in the animal studies. Three of these organisms were susceptible to penicillin (i.e., strains *S. sanguis* "Du," *S. sanguis* 1178, and *S. mitis* 750; MICs, ≤0.032 mg of penicillin per liter) and one was a penicillin-resistant strain (*S. mitis* 531, kindly provided by R. Moellering; MIC, 2 mg of penicillin per liter). In addition, 21 further streptococcal isolates recovered from patients with bacteremia were used in susceptibility tests comparing sparfloxacin with five other quinolones (listed in Table 1). The isolates were identified with API 20 Strep galleries (bioMérieux, Marcy l'Etoile, France). Unless otherwise stated, liquid cultures of bacteria were grown at 35°C without aeration in Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.) supplemented with 1% IsoVitaleX (BBL Microbiology Systems, Cockeysville, Md.).

Antibiotics. Sparfloxacin and pefloxacin were obtained from Rhône-Poulenc Rorer (Antony, France), ceftriaxone and fleroxacin were obtained from Roche Pharma (Reinach, Swit-

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zerland), penicillin G and ofloxacin were obtained from Hoechst-Pharma (Zurich, Switzerland), norfloxacin was obtained from Merck Sharp & Dohme (Glattbrug, Switzerland), and ciprofloxacin was obtained from Bayer AG (Wuppertal, Federal Republic of Germany). Solutions of antibiotics were prepared according to the manufacturers' instructions.

Antibiotic susceptibility and time-kill curves. MICs of antibiotics were determined by a previously described method (20). Briefly, series of tubes containing 1 ml of broth and twofold serial dilutions of antibiotics were inoculated with 10^5 to 10^6 CFU of bacteria. After incubation for 24 h at 35°C, the tubes were visually inspected and the MIC was defined as the lowest antibiotic concentration which inhibited visible bacterial growth.

For time-kill curves, series of tubes containing fresh prewarmed medium were inoculated with either 10^6 or 10^7 CFU/ml (final concentration) from an overnight culture of bacteria and were further incubated at 35°C. Immediately after inoculation, the tubes received antibiotics at final concentrations which approximated the levels of the drugs in human serum (see the Results section). Samples were removed from the tubes just before and at various times after antibiotic addition, serially diluted, and plated onto blood agar for colony counts. Antibiotic carryover was minimized by taking the following precautions. (i) For ceftriaxone, the samples were plated onto blood agar supplemented with 0.2% (vol/vol) of *Bacillus cereus* 569/H9 β-lactamase (penicillin amino-β-lactam hydrolase; Genzyme Diagnostics, Kent, England) and (ii) for sparfloxacin, bacterial plating was performed with a Spiral system inoculator device (Spiral system DS; Interscience, Saint-Nom, France) (18). The number of surviving CFU was determined after 48 h of incubation at 35°C. Antibiotics were considered bactericidal if they produced a $\geq$2-$\log_{10}$-unit reduction in the original inoculum after 24 h of incubation.

Production of endocarditis and installation of an infusion pump to deliver antibiotics to animals. Sterile aortic vegetations were produced in female Wistar rats (weight, 180 to 200 g) by a previously described method (11). Briefly, the animals were anesthetized and a polyethylene catheter (Guerbet Biomedical, Louvres, France) was inserted via the right carotid artery across the aortic valve. The catheter was secured with a silk ligature and was left in place for the remainder of the experiment. At the same time, an intravenous (i.v.) line consisting of a sterile silastic catheter (Dow Corning Corp., Midland, Mich.) was inserted via the jugular vein into the superior vena cava as described previously (9). The distal portion of the catheter was brought to the skin of the interscapular region and was connected to a programmable infusion pump (Pump 44; Harvard Apparatus, Inc., South Natick, Mass.) through a swivel that allowed the animals to move in an unrestrained fashion in their cages. The pump was set to deliver a volume of 0.2 ml of saline per h to keep the catheter open until the beginning of antibiotic treatment. No i.v. lines were placed in control animals.

Bacterial endocarditis was induced 24 h after catheterization by i.v. challenge of the animals with 0.5 ml of saline containing 10^7 CFU of either of the test organisms. This size of the inoculum was 10 to 100 times greater than the lowest size of the bacterial inoculum producing endocarditis in 90% of untreated control rats (i.e., the 90% infective dose).

Antibiotic treatment. Antibiotic therapy was started 48 h after bacterial challenge and lasted for either 3 or 5 days. Ceftriaxone was administered at changing flow rates with the programmable infusion pump as described above and by Blatter et al. (4). Sparfloxacin for i.v. use is a developmental form of the drug that produces kinetics in human serum which have been mathematically predicted, assuming both (i) that a 400-mg i.v. injection of the compound would produce peak antibiotic concentrations of ca. 4 mg/liter in serum after 1 h and (ii) that the half-life of the drug in serum is 18 to 20 h. These predicted drug levels could be mimicked in rats by administering subcutaneous injections of 40 mg of sparfloxacin per kg of body weight four times a day.

Antibiotic levels in sera of rats. The levels of sparfloxacin or ceftriaxone in the sera of groups of 5 to 10 infected rats were determined at several time points during and after antibiotic administration. Blood samples were drawn from the retroorbital sinus into microhematocrit tubes (Clay Adams, Parsippany, N.Y.). Antibiotic concentrations were measured by the agar diffusion method with *Escherichia coli* Kp 1976-712 (kindly provided by Rhône-Poulenc Rorer Laboratories) for sparfloxacin and *E. coli* ATCC 25922 for ceftriaxone. For standard curves, antibiotics were diluted in pooled rat serum. The limits of detection of the bioassay were ca. 0.15 mg/liter for sparfloxacin and 3 mg/liter for ceftriaxone.

Evaluation of infection. Control rats were sacrificed at the treatment onset (i.e., 48 h after inoculation) in order to quantify both the incidence and the severity of valvular infection at the start of therapy. Treated rats were sacrificed 24 h after administration of the last antibiotic dose, a time at which no residual antibiotic could be detected in the blood. The valvular vegetations were removed under sterile conditions, weighed, homogenized in 1 ml of saline, and serially diluted before plating for colony counts. Quantitative blood cultures and cultures of the spleen were performed in parallel. The numbers of colonies growing on the plates were determined after 48 h of incubation at 35°C, and the bacterial densities in the vegetations were expressed as $\log_{10}$ CFU per gram of tissue. Vegetations were considered sterile if bacterial titers were less than 2 $\log_{10}$ CFU/g. For calculation of the median number of CFU per gram of vegetation, such vegetations were considered to contain 2 $\log_{10}$ CFU/g.

Screening for emergence of sparfloxacin-resistant bacteria during antibiotic treatment in vivo. To evaluate the emergence of sparfloxacin-resistant organisms during drug treatment, 0.1-ml portions of each undiluted vegetation homogenate (from sparfloxacin-treated rats) were plated onto both plain blood agar and blood agar supplemented with either 2 or 4 mg of sparfloxacin per liter, i.e., four to eight times the MICs for the test organisms. This screening was not performed for ceftriaxone.

Statistical analysis. The chi-square test with Yates' correction was used to compare the incidence of valvular infections. Nonparametric analysis by the Wilcoxon Mann-Whitney test was used to compare the bacterial counts in the vegetations. All reported significance levels are two-tailed.

RESULTS

Susceptibility studies and time-kill curves. The MICs of sparfloxacin for the four isolates tested in vivo were between 0.25 and 0.5 mg/liter. Relatively low MICs of this compound were also observed for 21 additional streptococci isolates, as shown in Table 1. It can be seen that the MICs of sparfloxacin for these bacteria were eight times or more greater than those of the five other quinolones, including ciprofloxacin, ofloxacin, pefloxacin, norfloxacin, and fleroxacin. Therefore, against this restricted number of streptococci, sparfloxacin appeared to be more efficacious than other antibiotics of this group of compounds. In addition, sparfloxacin was also bactericidal when it was tested in broth cultures in vitro, as shown by the results of the time-kill curves depicted in Fig. 1.

TABLE 1. Comparative activities of sparfloxacin and other quinolones against 25 clinical isolates of streptococci

Drug	MIC (mg/liter)[a]		
	50%	90%	Range
Sparfloxacin	0.12	0.5	0.04–8
Ciprofloxacin	1	4	0.12–8
Ofloxacin	1	4	0.12–4
Pefloxacin	2	8	0.06–16
Norfloxacin	4	8	0.25–16
Fleroxacin	4	8	0.12–16

[a] The MICs for the four organisms tested in animal experiments are specified in the text (see Results section). 50% and 90%, MICs at which 50 and 90% of isolates are inhibited, respectively.

In comparison, ceftriaxone had generally lower MICs than those of sparfloxacin for the penicillin-susceptible strains tested in vivo (i.e., MIC, 0.032 to 0.064 mg of ceftriaxone/liter) but not for the penicillin-resistant strain *S. mitis* 531 (MIC, 2 mg/liter). Ceftriaxone used at high concentrations (i.e., ca. 100 times the MIC) in broth cultures was also bactericidal, but no more so than sparfloxacin (Fig. 1). In addition, since ceftriaxone is highly bound to proteins (ca. 90%) (22) we also tested its in vitro bactericidal effect in the presence of 50% rat serum when trough levels of the drug in blood were used. This was important to ensure that a sufficient amount of free ceftriaxone was actually available in vivo at trough levels to kill bacteria or inhibit growth. The closed diamonds in Fig. 1 show that bacterial killing under these conditions was similar to killing with higher drug concentrations for each of the four microorganisms.

Antibiotic levels in serum. The kinetics in human serum produced by a 2-g i.v. injection of ceftriaxone could be simulated in rats by injecting a total of 1.06 g of antibiotic every 24 h through the infusion pump at changing flow rates (see Materials and Methods and reference 4). This resulted in peak and trough ceftriaxone levels in rat serum (mean ± standard deviation of five to nine determinations in individual animals) which were 261 ± 27 mg/liter at 30 min and 15.8 ± 5 mg/liter at 24 h, respectively. For comparison, i.v. administration of 2 g of ceftriaxone to humans results in peak and trough levels in serum of 256 ± 16 and 15 ± 3.9 mg/liter at 30 min and 24 h, respectively (17).

As mentioned in Materials and Methods, the kinetics in human serum following an i.v. injection of 400 mg of the new parenteral form of sparfloxacin (i.e., the total dose of sparfloxacin expected to be given in single daily injection to adult humans) was predicted by calculation. The expected peak and trough levels in human serum produced by this dosage are 4 to 6 mg/liter at 1 h and 1.5 to 2.5 mg/liter at 24 h, respectively. These drug concentrations could be mimicked in rats by subcutaneous injection of 40 mg of sparfloxacin per kg four times a day. This schedule reliably produced peak and trough levels of total drug (mean ± standard deviation of 5 to 10 determinations in individual animals) of 3.7 to 5.5 and 2.1 to

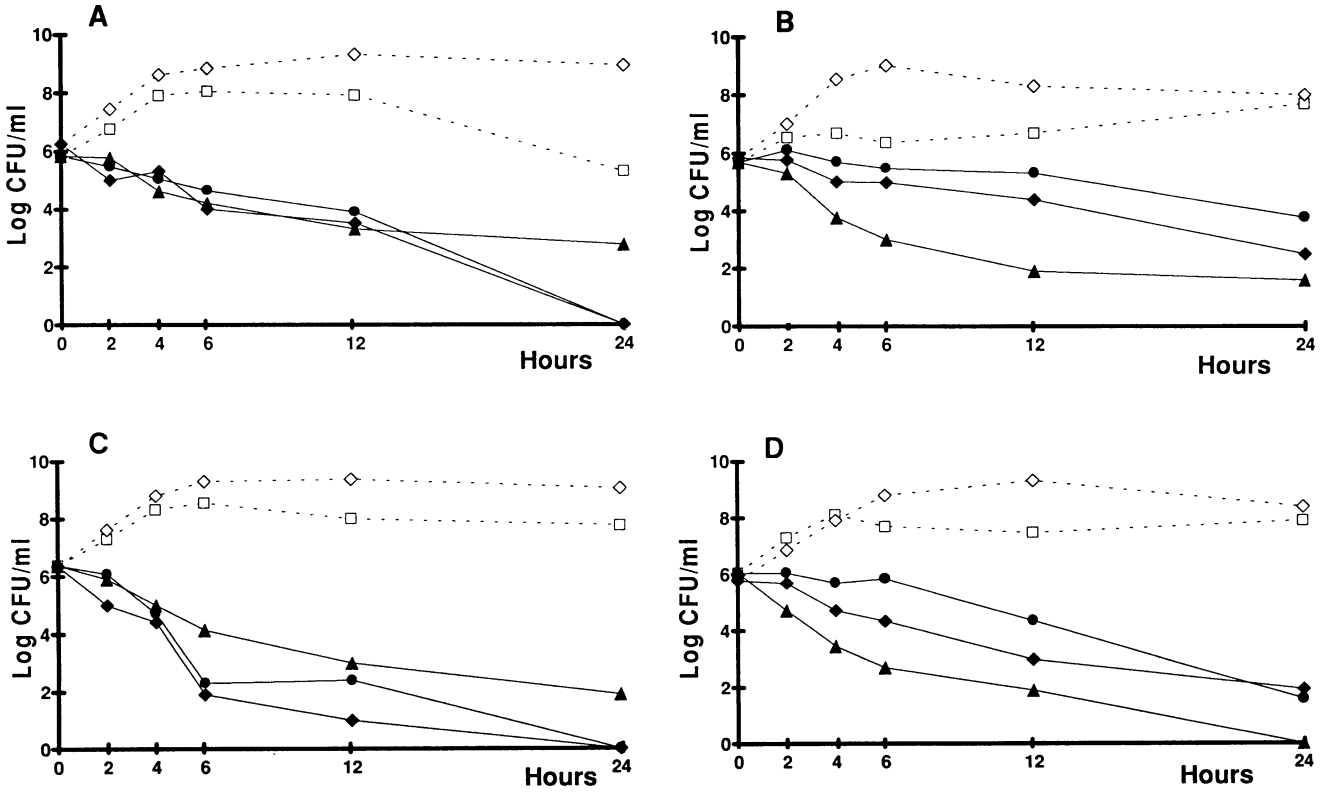

FIG. 1. In vitro time-kill experiments for *S. sanguis* "Du" (A), *S. sanguis* 1178 (B), *S. mitis* 750 (C), and *S. mitis* 531 (D). Overnight cultures of bacteria were used to inoculate tubes containing fresh prewarmed medium (as described in Materials and Methods), and either sparfloxacin at 4 mg/liter (closed triangles), ceftriaxone at 200 mg/liter (closed circles), or ceftriaxone at 15 mg/liter (in the presence of 50% rat serum; closed diamonds) was added thereafter. Control tubes in the presence of 50% rat serum (open diamonds) or not (open squares) received no drug. Note that experiments repeated with 10 times larger inocula (i.e., 10^7 instead 10^6 CFU/ml) gave similar bacterial killing profiles.

TABLE 2. Outcome of 3-day treatment of experimental endocarditis caused by three strains of penicillin-susceptible streptococci and one penicillin-resistant streptococcal strain

Strain[a]	Regimen					
	Control		Sparfloxacin		Ceftriaxone	
	Median log CFU/g of vegetation (range)	No. of infected rats/total no. (%)	Median log CFU/g of vegetation (range)	No. of infected rats/total no. (%)	Median log CFU/g of vegetation (range)	No. of infected rats/total no. (%)
S. sanguis "Du"	9.05 (8.5–9.4)	8/8 (100)	6.95 (≤2–9.1)[b]	21/24 (87)	2.53 (≤2–5.4)[b,c]	7/12 (58)[b]
S. sanguis 1178	8.86 (7.3–9.3)	4/4 (100)	5.71 (2.6–7.4)[b]	13/13 (100)	3.45 (≤2–6.2)[b,c]	4/6 (67)
S. mitis 750	8.88 (7.7–9.3)	5/5 (100)	4.56 (≤2–7.4)[b]	13/18 (72)	3.44 (≤2–6.5)[b]	6/7 (86)
S. mitis 531	9.19 (7.4–9.5)	11/11 (100)	≤2 (≤2–6.2)[b,c]	10/27 (37)[b,c]	8.54 (4.8–9.1)	9/9 (100)

[a] *S. mitis* 531 was penicillin resistant. The other three organisms were penicillin susceptible.
[b] $P < 0.001$ compared with controls.
[c] $P < 0.05$ compared with the other drug.

3.6 mg/liter at 1 and 24 h, respectively, in the animals. The levels of sparfloxacin were measured in serum over the whole treatment interval, and no accumulation of antibiotic was observed in the animals.

Therapeutic outcomes in rats with experimental endocarditis. Table 2 shows that after 3 days of treatment, sparfloxacin was generally less effective than ceftriaxone in sterilizing the vegetations infected with penicillin-susceptible strains of streptococci. Nevertheless, 3 days of sparfloxacin treatment, which is a short course of therapy, resulted in a significant reduction in the valvular bacterial titer. In contrast to this observation, Table 2 also shows that sparfloxacin was much more effective than ceftriaxone against the penicillin-resistant isolate *S. mitis* 531. Ceftriaxone treatment totally failed against this organism in vivo, even though the peak and trough levels of total drug in serum (i.e., 256 and 15 mg/liter, respectively) were theoretically much higher than the drug's MIC for this strain. It is possible that the high level of ceftriaxone protein binding (ca. 90%) played a role in this lack of efficacy.

In spite of these differential effects, cultures of the blood and spleen of all of the animals infected with penicillin-susceptible strains were already sterile at 3 days of therapy, independently of the antibiotic that they received. In contrast, the blood and spleens of 100% of untreated control animals were already heavily infected at time zero of therapy (e.g., spleen cultures contained 4.35 ± 0.61 $\log_{10}$ CFU/g of tissue [mean ± standard deviation of 23 determinations]).

Since vegetations are devoid of cellular host defense mechanisms (1, 8), it is likely that in such an environment (i.e., without the assistance of blood leukocytes) antibiotics may require more time to sterilize the infected lesions. Therefore, in a second series of experiments the duration of antibiotic therapy was prolonged from 3 to 5 days. The results of those studies are depicted in Fig. 2. Prolongation of therapy to 5 days resulted in a further and substantial decrease in the bacterial titers in the vegetations of both treatment groups. At that time, the residual difference in bacterial titers between sparfloxacin- and ceftriaxone-treated rats was no longer significant (Fig. 2). It is also noteworthy that none of the viable bacteria recovered from sparfloxain-treated animals became resistant to the latter compound by day 5 (as determined on plates containing greater than or equal to four times the MICs for the organisms). Therefore, it is likely that further prolongation of treatment with either antibiotic would have resulted in the eventual sterilization of all of the infected valves.

DISCUSSION

The results of the present study show that a new, investigational, i.v. form of sparfloxacin given at doses that mimic the levels in human serum is effective for the treatment of experimental endocarditis caused by penicillin-susceptible and -resistant clinical isolates of streptococci. These results in animals correlated with the good in vitro activity of the compound, which had relatively low MICs for all four test organisms and was at least as bactericidal as ceftriaxone in time-kill experiments. Low sparfloxacin MICs for streptococci were also confirmed for an additional panel of 21 strains isolated from patients with streptococcal endocarditis or bacteremia. These bacteria were greater than or equal to eight times more susceptible to growth inhibition by sparfloxacin than by the other quinolones tested. Such good activity of sparfloxacin against gram-positive cocci was also reported by others in the literature (5, 14, 24).

However, while sparfloxacin effectively decreased the bacterial titers in vegetations after 3 and 5 days of treatment, the drug was generally slower than ceftriaxone in its ability to reduce valvular infections caused by penicillin-susceptible organisms. In contrast, both compounds achieved rapid sterilization of the blood and the spleen cultures, suggesting that both drugs rapidly eradicated bacteria in the presence of phagocytic cells. Therefore, the explanation for the differential drug efficacies in the valvular lesions probably relies on the ability of the individual antibiotic to achieve bacterial killing inside the vegetation, an environment known to be virtually devoid of cellular host defense mechanisms (1, 8).

This differential efficacy in the vegetation was not reflected by discrepancies between the bactericidal activities of the drugs in vitro, as shown by the rather similar bactericidal effects of both antibiotics in time-kill experiments. In addition, no major difference in the drugs' abilities to diffuse from the serum into the vegetation was found, which could explain the faster in situ killing of penicillin-susceptible strains by ceftriaxone than by sparfloxacin. Indeed, after injection, the concentration of sparfloxacin in serum and in the vegetation rapidly equilibrated (with kinetics comparable to those of β-lactam antibiotics), as demonstrated both by diffusion measurements of radioactively labeled drugs (formally published for ceftriaxone and published in an abstract form for sparfloxacin [6, 7]) and by measurement of the drug's bioactivity in cardiac lesions determined in the present study (data not presented).

An alternative explanation for the slower bactericidal effect of sparfloxacin in animals might rely on differences in the

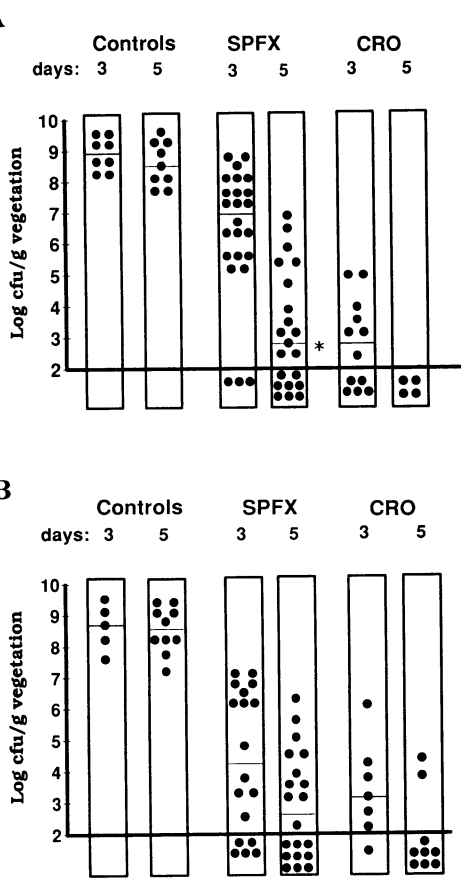

FIG. 2. Outcomes of 3 and 5 days of treatment with either sparfloxacin (SPFX) or ceftriaxone (CRO). *S. sanguis* "Du" (A) and *S. mitis* 750 (B) were two penicillin-susceptible isolates chosen for their relatively poor responses to sparfloxacin and relatively good responses to ceftriaxone after 3 days of therapy (Table 2). Each individual dot in the figure represents the bacterial density in the vegetation of separate animals. The duration of treatment and treatment groups are indicated at the top. Bars on the columns indicate the median values of vegetation bacterial densities. *, $P < 0.05$ when comparing the results of 3 days versus 5 days of treatment.

gradient of antibiotic concentrations between the vascular compartment and the core of the vegetation just after drug injection. Indeed, even considering the high level of protein binding of ceftriaxone (i.e., 90%), the peak levels of the drug in serum (peak of total antibiotic, ca. 260 mg/liter) were still greater than or equal to 1,000 times its MIC for penicillin-susceptible streptococci. In comparison, peak levels of the 40% protein-bound sparfloxacin (13) (peak of total antibiotic, ca. 4 mg/liter) were at best five times greater than the antibiotic's MIC for the infecting bacteria. Thus, it is conceivable that an inhibitory (and ultimately bactericidal) titer of antibiotic in the vegetation was achieved less rapidly after sparfloxacin injection than after ceftriaxone injection.

Whether such a disadvantageous therapeutic margin might be genuinely detrimental during sparfloxacin (versus ceftriaxone) therapy remains to be determined. Indeed, while peak and trough levels of sparfloxacin in serum were "only" five and two times greater than the MIC, the drug was effective against all four organisms tested. In comparison, ceftriaxone treatment totally failed against infections caused by a penicillin-resistant isolate (MIC of ceftriaxone, 2 mg/liter), in spite of levels of free antibiotic in serum which were theoretically up to 10 times greater than the MIC over the whole treatment period. Thus, while determination of the serum-antibiotic-level/strain susceptibility ratio may predict the in vivo efficacies of structurally related compounds (12, 16), this may not be true for comparisons of mechanistically unrelated antibiotics, even when both molecules diffuse thoroughly into the vegetation.

The most obvious and realistic determination of in situ drug efficacy would be the direct measurement of inhibitory and bactericidal antibiotic titers in the vegetation environment. While such a test has yet to be established in vitro, its results can already be foreseen by the even more realistic results of in vivo therapeutic experiments.

In conclusion, it appears that sparfloxacin treatment administered at doses that mimic the levels achievable in human serum by i.v. administration of the drug is effective for the treatment of experimental endocarditis caused by both penicillin-susceptible and penicillin-resistant streptococci. In addition, the good activity of sparfloxacin against gram-positive cocci is not limited to streptococci, since the drug was also effective against experimental endocarditis caused by methicillin-resistant *Staphylococcus aureus* and enterococci (3, 23). Thus, this new quinolone may become useful as an alternative to β-lactams or other anti-gram-positive antibiotics for the treatment of severe infections caused by such organisms. A major advantage of the compound is its prolonged half-life in serum, which permits simplified therapeutic schedules (with a single daily administration) and which may ultimately allow for the treatment of patients with severe infections on an outpatient basis. However, this advantage must be weighed against the fact that broad-spectrum antibiotic therapy is not necessarily desirable for infections caused by specific organisms, since it will also eradicate most of the patient's natural flora and carries the risk of selecting for antibiotic resistance in other (essentially digestive) bacteria.

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