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In vitro activity of moxifloxacin compared to other antimicrobials against streptococci isolated from iatrogenic oral bacteremia in Spain

I. Tomás[1], M. Álvarez[2], J. Limeres[1], J. L. Otero[3], E. Saavedra[2], C. López-Meléndez[2], P. Diz[1]

[1]Department of Special Needs, School of Medicine and Dentistry, Santiago de Compostela University, [2]Research Laboratory, Department of Clinical Microbiology, Xeral-Cíes Hospital, Vigo, [3]Department of Biostatistics, School of Medicine and Dentistry, Santiago de Compostela University, Spain

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Background/aims: Systemic dissemination of oral bacteria to distant body sites may be the cause of focal infections. The unsuitable use and overexposure to antimicrobial therapy in clinical dental practice may contribute to the worldwide problem of antimicrobial resistance. The aim of this study was to determine the susceptibilities of streptococci isolated from the bloodstream after dental extractions against penicillin, ampicillin, amoxicillin, erythromycin, clindamycin, and a new fluoroquinolone, moxifloxacin.

Patients and methods: Eighty-four patients who required dental extractions were studied. Venous blood samples were collected from each patient at baseline (before dental manipulation) and 30 s after dental extractions. The samples were processed in the Bactec 9240. The isolated bacteria were identified by conventional microbiological techniques. The antimicrobial susceptibility of 81 streptococci was determined by the *E*-test method. The NCCLS performance standards were followed.

Results: 88.9–92.5% of the streptococci were sensitive to beta-lactam agents tested with a minimum inhibitory concentration $(MIC)_{90s}$ ranging from 0.094 to 0.19 mg/l. The resistance to erythromycin and clindamycin was 40.8% ($MIC_{90HR} = 256$ mg/l) and 21% ($MIC_{90HR} = 256$ mg/l), respectively. The MIC_{90} to moxifloxacin was 0.125 mg/l.

Conclusion: Most of the streptococci isolated from the bloodstream after dental extractions were susceptible *in vitro* to penicillin, ampicillin, and amoxicillin. The high percentage of streptococci resistant to erythromycin and clindamycin could restrict their usefulness as prophylactic drugs. All the isolates showed a low MIC of moxifloxacin *in vitro*, making it a promising antimicrobial alternative for the prevention of streptococcal focal infections associated with certain dental manipulations, when the administration of beta-lactam agents is not indicated.

Key words: bacteremia; dental extractions; moxifloxacin; streptococci

Pedro Diz Dios, C./Panama 2; 2° dcha, 36203 Vigo, Spain
Tel.: +34 981 563100;
fax: +34 981 562226;
e-mail: pdiz@usc.es

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It has been shown that 55–100% of all dental procedures accompanied by bleeding of the oral mucosa are associated with bacteremia, mainly streptococcal in nature (14). Recently, Roberts et al. (27) demonstrated that even some bloodless conservative dental procedures provoke bacteremia in a considerable number of cases. Systemic dissemination of oral

bacteria to distant body sites may be the cause of focal infections such as bacterial endocarditis, brain abscesses, and other life-threatening infections. The most frequently isolated bacteria are viridans streptococci (10, 19, 22).

The use of antimicrobial prophylaxis in patients at risk of focal infections who undergo certain dental procedures is a reasonably well-accepted practice (12). Beta-lactam agents have traditionally been considered the antibiotic of choice. In patients allergic to penicillin, alternative antibiotics such as erythromycin, newer macrolides (azithromycin, clarithromycin), and clindamycin have been proposed (4, 5, 36).

Several studies carried out in different countries have shown that general dental practitioners sometimes prescribe antimicrobials inappropriately, with incorrect doses and duration of treatment, and often in clinical situations which do not warrant their use (7, 17). This unsuitable use and overexposure to antimicrobial therapy in clinical dental practice may increase the emergence of resistance in oral bacteria, contribute to the worldwide problem of antimicrobial resistance (24).

The aim of this study was to determine the susceptibilities of streptococci isolated from the bloodstream after dental extractions to different antimicrobials frequently used in dentistry and to a new 8-methoxy-fluoroquinolone, moxifloxacin.

Patients and methods

Study population

The study population was composed of patients who required dental extractions between September 2000 and June 2002. The exclusion criteria were as follows:

- under 18 years of age;
- had received antimicrobials during the previous 3 months;
- presented some type of congenital or acquired immunodeficiency or systemic disease predisposing to infection.

Applying these criteria, 84 patients were selected (45 males, 39 females) with a mean age of 25.1 ± 11.2 years (range 18–57 years).

The protocol was approved by the Institutional Review Board of the School of Medicine, Dentistry (Santiago de Compostela University). Written informed consent was obtained from all the participants.

Blood drawing and bacterial isolates

Following skin preparation with 1% povidone-iodine solution, an intravenous cannula was inserted into a vein in the antecubital fossa of either arm using a standard aseptic technique. Venous blood samples (10 ml) were collected from each patient at baseline (before dental manipulation) and 30 s after dental extractions. The recommendations of the Spanish Society of Infectious Diseases and Clinical Microbiology were followed (31).

Each blood sample was divided equally into aerobic, anaerobic blood culture bottles, Bactec plus aerobic/f, and Bactec plus anaerobic/f (Becton Dickinson, Company, Sparks, MD). In the laboratory, the bottles were processed in the Bactec 9240 (Becton Dickinson). When an aerobic bottle was identified as positive, a Gram stain was performed. The bottle was subcultured in blood agar, chocolate agar incubated under 5–10% CO_2, and MacConkey agar incubated aerobically. The same procedure was followed for the positive anaerobic bottles as for the aerobic ones, including subculture on Schaedler's agar and incubation in an anaerobic atmosphere. The isolated bacteria were identified by conventional microbiological techniques (20). Viridans streptococci were identified as aerobic cocci that display chains in the Gram stain, were negative for beta-hemolysis (except some *Streptococcus anginosus* group), were catalase negative, optochin-resistant, pyrrolidonyl arylamidase-negative, leucine aminopeptidase-positive, and did not grow in 6.5% NaCl broth. The strains were classified in five groups (32, 33). Strains that showed at least one reaction different from this pattern but which were still catalase-negative, negative for beta-hemolysis and gram-positive in chains, were classified as non viridans streptococci (9).

Antimicrobial susceptibility testing

Minimum inhibitory concentrations (MICs) were determined by the *E*-test method (AB Biodisk, Solna, Sweden) according to the manufacturer's instructions. The NCCLS performance standards were followed (21). The MIC interpretations were done in accordance with published guidelines (21). The antimicrobials tested were penicillin, amoxicillin, ampicillin, erythromycin, clindamycin, and moxifloxacin. The MIC_{50} and MIC_{90} were defined as the MICs at which 50% and 90% of the isolates were inhibited. The qualitative interpretative criteria of susceptible (S), intermediately resistant (IR), and highly resistant (HR) were related to the MIC_{50} and the MIC_{90} in each of the qualitative categories, defining the $MIC_{50\ S,\ IR}$ and $_{HR}$, and the $MIC_{90\ S,\ IR}$ and $_{HR}$ in which 50% or 90% of the strains S, IR, and HR were inhibited.

Statistical analysis

The data were analyzed by the SPSS version 10.0 for Windows. The Chi-squared test was used to attribute statistical significance to susceptibility rate differences (susceptible, intermediately or highly resistant) to all antimicrobials (except moxifloxacin) among the different streptococcal groups. The Kappa statistic and a nonparametric Mann–Whitney test were applied to assess the antimicrobial cross-resistance. To compare the MICs to moxifloxacin between the different streptococcal groups, a nonparametric Kruskal–Wallis test was performed. A P-value of <0.05 was considered statistically significant.

Results

The prevalence of bacteremia in 84 patients was 10% at baseline and 93% at 30 s after dental extractions. Of the 168 blood samples, 86 (51%) were identified as positive cultures. In all, 89.3% of the positive blood cultures yielded a single species, 10.1% yielded two species, and 0.6% yielded four species.

A total of 107 strains were isolated (Table 1), 76% of them streptococci (3 strains isolated at baseline and 78 isolated 30 s after dental extractions). The following streptococcal groups were identified:

- *Streptococcus mitis* group: 35 strains (43.2%);
- *S. anginosus* group: 24 strains (29.6%);
- other viridans streptococci (*mutans, salivarius* groups): 11 strains (13.6%);
- non viridans streptococci: 11 strains (13.6%).

Following the breakpoint criteria established by the NCCLS (21), 36 (44.5%) of the streptococci showed decreased susceptibility (intermediately or highly resistant) to at least one of the antimicrobials studied. Fourteen (17.3%) strains were resistant to one antimicrobial, 13 (16.1%) to two antimicrobials, 6 (7.4%) to three antimicrobials, 1 (1.2%) to four antimicrobials, and 2 (2.5%) to five antimicrobials. None of the isolates was resistant to all six antimicrobials tested.

In all, 88.9% ($MIC_{90S} = 0.094$ mg/l), 92.5% ($MIC_{90S} = 0.19$ mg/l), and 92.5% ($MIC_{90S} = 0.125$ mg/l) of streptococci were susceptible to penicillin, ampicillin, and amoxicillin, respectively. *S. mitis* group showed the highest percentage of intermediately penicillin-resistant strains

Table 1. Bacteria isolated in the positive blood cultures performed after dental extractions (n = 107)

Isolated bacteria	n (%)
Streptococcus spp.[a]	81 (76%)
Neisseria spp.[b]	7 (6.5%)
Gemella spp.[c]	4 (3.7%)
Fusobacterium spp.[d]	3 (2.8%)
Peptostreptococcus spp.[e]	3 (2.8%)
Actinomyces spp.[f]	3 (2.8%)
Veillonella spp.[g]	2 (1.8%)
Bacteroides spp.[h]	1 (0.9%)
Enterococcus spp.[i]	1 (0.9%)
Prevotella spp.[j]	1 (0.9%)
Eikenella spp.[k]	1 (0.9%)
Total	107 (100%)

[a]Isolated *Streptococcus* spp. 35 *S. mitis* group, 24 *S. anginosus* group, 11 *Streptococcus mutans*, *Streptococcus salivarius* groups, 11 non viridans streptococci.
[b]Isolated *Neisseria* spp. 3 *Neisseria cinerea*, 2 *Neisseria lactamica*, 1 *Neisseria mucosa*, 1 *Neisseria subflava*.
[c]Isolated *Gemella* spp. 4 *Gemella morbillorum*.
[d]Isolated *Fusobacterium* spp. 1 *Fusobacterium nucleatum*, 1 *Fusobacterium varium*, 1 *Fusobacterium necrophorum*.
[e]Isolated *Peptostreptococcus* spp. 1 *Peptostreptococcus magnus*, 1 *Peptostreptococcus micros*, 1 *Peptostreptococcus anaerobius*.
[f]Isolated *Actinomyces* spp. 3 *Actinomyces odontolyticus*.
[g]Isolated *Veillonella* spp. 2 *Veillonella parvula*.
[h]Isolated *Bacteroides* spp. 1 *Bacteroides fragilis*.
[i]Isolated *Enterococcus* spp. 1 *Enterococcus casseliflavus*.
[j]Isolated *Prevotella* spp. 1 *Prevotella corporis*.
[k]Isolated *Eikenella* spp. 1 *Eikenella corrodens*.

Table 2. Susceptibility rate, MIC_{50}, MIC_{90}, range of MICs for 81 streptococci isolated from blood cultures performed after dental extractions

Antimicrobial	No. of strains (%)	MIC_{50}, mg/l	MIC_{90}, mg/l	Range, mg/l
Penicillin				
Total		0.032	0.19	0.004–4
S	72 (88.9%)	0.032	0.094	0.004–0.125
IR	8 (9.9%)	0.25	2	0.19–2
HR	1 (1.2%)	4	4	4
Ampicillin				
Total		0.047	0.25	0.016–2
S	75 (92.5%)	0.047	0.19	0.016–0.25
IR	6 (7.5%)	0.75	2	0.047–2
HR	–	–	–	–
Amoxicillin				
Total		0.047	0.25	0.016–4
S	75 (92.5%)	0.047	0.125	0.016–0.25
IR	6 (7.5%)	1.5	4	0.38–4
HR	–	–	–	–
Erythromycin				
Total		0.064	256	0.016–256
S	48 (59.2%)	0.023	0.094	0.016–0.25
IR	–	–	–	–
HR	33 (40.8%)	16	256	1–256
Clindamycin				
Total		0.047	256	0.016–256
S	63 (77.8%)	0.032	0.094	0.016–0.25
IR	1 (1.2%)	0.5	0.5	0.5
HR	17 (21%)	256	256	12–256
Moxifloxacin				
NA		0.094	0.125	0.002–0.5

S = Susceptible. IR = Intermediately resistant. HR = Highly resistant.
MIC_{50} and MIC_{90}: MICs at which 50% and 90% of the isolates are inhibited, respectively.
MIC breakpoints were as follows: susceptible to penicillin, MIC ≤0.12 mg/l; intermediately resistant to penicillin, MIC 0.25–2 mg/l; highly resistant to penicillin, MIC ≥4 mg/l; susceptible to ampicillin or amoxicillin, MIC ≤0.25 mg/l; intermediately resistant to ampicillin or amoxicillin, MIC 0.5–4 mg/L; highly resistant to ampicillin or amoxicillin, MIC ≥8 mg/l; susceptible to erythromycin, MIC ≤0.25 mg/l; intermediately resistant to erythromycin, MIC 0.5 mg/l; highly resistant to erythromycin, MIC ≥1 mg/l; susceptible to clindamycin, MIC ≤0.25 mg/l; intermediately resistant to clindamycin, MIC 0.5 mg/l; highly resistant to clindamycin, MIC ≥1 mg/l (21).
NA, not applicable.

(11.4%) and the only highly resistant strain. No streptococci highly resistant to ampicillin or amoxicillin were isolated. Resistance to erythromycin was found for 40.8% ($MIC_{90\ HR}$ = 256 mg/l) of streptococci. *S. mitis* group showed the highest resistance rate to erythromycin (57.2%), followed by non viridans streptococci (36.4%), *S. anginosus* group (33.3%), and other viridans streptococci (18.2%). Resistance to clindamycin was found in 21% ($MIC_{90\ HR}$ = 256 mg/l) of the streptococci, comprising 27.3% of non viridans streptococci; 22.9% of *S. mitis* group; 20.8% of *S. anginosus* group; 9.1% of other viridans streptococci.

There were no statistically significant differences in the susceptibility to beta-lactam agents, erythromycin, or clindamycin among the different streptococcal groups tested.

The MIC_{90} to moxifloxacin of isolated streptococci was 0.125 mg/l. There were no statistically significant differences in the MIC_{90} values in the different streptococcal groups.

The susceptibility rates, MIC_{50}, MIC_{90}, and ranges of MICs for 81 streptococci against the six antimicrobial agents tested are given in Table 2.

Among the streptococci that were intermediately (MIC = 0.25–2 mg/l) or highly resistant to penicillin (MIC ≥ 4 mg/l), 62.5% were also intermediately resistant to ampicillin (Kappa = 0.687) and amoxicillin (Kappa = 0.686). All streptococci that were intermediately resistant to ampicillin were intermediately resistant to amoxicillin (Kappa = 1.000). Of the streptococci that were not susceptible (intermediately or highly resistant) to any beta-lactam antimicrobial, 70% were also resistant to erythromycin (MIC ≥1 mg/l) (Kappa = 0.165) and 60% were resistant to clindamycin (MIC ≥1 mg/l) (Kappa = 0.319). The resistance (intermediately or highly resistant) to any beta-lactam antimicrobial was significantly associated with resistance to other beta-lactam agents ($P < 0.001$), erythromycin ($P < 0.05$), and clindamycin ($P < 0.05$). Of the erythromycin-resistant streptococci, 51.5% were also resistant to clindamycin (Kappa = 0.530) ($P < 0.001$). Of the 14 isolates that showed an MIC to erythromycin of >256 mg/l, 13 (92.8%) showed cross-resistance to clindamycin. All the clindamycin-resistant strains, except one, were also resistant to erythromycin (Kappa = 0.530) ($P < 0.001$).

The MIC_{90} to moxifloxacin (MIC_{90} = 0.5 mg/l) of streptococci non-susceptible to any beta-lactam agent was significantly higher than that of susceptible streptococci (MIC_{90} = 0.125 mg/l) (Mann–Whitney test, $P < 0.05$). There were no statistically significant differences in the MIC_{90} values to moxifloxacin among susceptible or resistant isolates to erythromycin and clindamycin.

Discussion

Various authors (6, 23) have found elevated percentages of viridans streptococci isolated from blood and pharyngeal exudates that were intermediately or highly resistant to beta-lactam antibiotics. By contrast, our results showed that the majority of the streptococci were susceptible to

beta-lactams. As in this study, Hall et al. (11) and Roberts et al. (28) found that 90% of viridans streptococci isolated from blood cultures following dental procedures were susceptible to beta-lactams. In accordance with previous studies (2), *S. mitis* group showed a lower susceptibility rate to penicillin than the other streptococci.

Alcaide et al. (2) reported that resistance to penicillin is frequently associated with reduced susceptibility to other beta-lactam agents. Our results also showed cross-resistance among beta-lactams, since 62.5% of the streptococci with reduced susceptibility (intermediately or highly resistant) to penicillin also showed reduced susceptibility to ampicillin and amoxicillin. Several studies have demonstrated that penicillin-resistant viridans streptococci showed a high resistance rate to erythromycin (1, 16). In this study a high percentage of streptococci with reduced susceptibility (intermediately or highly resistant) to any beta-lactam were also resistant to erythromycin and clindamycin. This suggests that bacteria that are resistant to one drug are likely to become resistant to others independently of the mechanism of resistance (18).

Although some authors have found a high activity of erythromycin against streptococci (13, 28), it has recently been shown that 94% of Spanish adults carry erythromycin-resistant commensal streptococci in their pharynx (26). In agreement with other studies (16, 39), in our series, 41% of the isolated streptococci were resistant to erythromycin. In accordance with Doern et al. (6), the *S. mitis* group strains were more resistant to erythromycin than the other streptococci.

Among isolates from blood cultures following oral surgical procedures, some authors (13, 28) found that 92–99% of streptococci were susceptible to clindamycin. Conversely, our study supports the results of Teng et al. (38), who detected 20–50% clindamycin resistance in viridans streptococci that had been isolated from different sources from patients with clinically significant infections.

In Spain, Aracil et al. (3) showed that less than 20% of the erythromycin-resistant viridans streptococci in pharyngeal samples presented the MSL_B phenotype. Conversely, also in a Spanish series, Pérez-Trallero et al. (26) found that similar percentages of erythromycin-resistant streptococci harbored the M and MSL_B phenotypes (49.8% and 50.2%, respectively). In our study, half of the erythromycin-resistant isolates were also resistant to clindamycin, suggesting that the M and MSL_B phenotypes may show similar prevalences. It has been observed that the MICs of macrolides were significantly higher for the strains with the MSL_B phenotype than for the strains with the M phenotype (26, 29). In the present series, all but one of the streptococci with MICs to erythromycin of >256 mg/l showed cross-resistance to clindamycin.

Moxifloxacin is an 8-methoxy-fluoroquinolone agent. Its clinical efficacy rate is 90–96% in community-acquired pneumonia (15), acute exacerbations of chronic bronchitis (34), and acute sinusitis (35). It has been also shown to be of potential utility for the treatment of pneumococcal otitis media (40) and bacterial skin infections (25).

Recently, Sobottka et al. (37) found that moxifloxacin has good *in vitro* activity against odontogenic pathogens. In their work, the MIC_{90} of viridans streptococci was 0.5 mg/l (range 0.064–0.5 mg/l). In our study, the MIC_{90} of moxifloxacin was 0.125 mg/l for all the isolated streptococci.

Espósito et al. (8) and Rodríguez Avial et al. (30) compared the *in vitro* activity of moxifloxacin with that of other fluoroquinolones against different erythromycin-resistant phenotypes of group A beta-hemolytic *Streptococcus* isolated from children affected by acute pharyngotonsillitis, and of viridans streptococci isolated from blood, respectively. In both studies, the activity of moxifloxacin was enhanced compared with the other fluoroquinolones regardless of the macrolide-resistant phenotypes. In the present series, moxifloxacin showed a low MIC *in vitro* against all isolated strains; this was not related to the resistance to any of the antimicrobials tested, with the exception of beta-lactam agents. For the non-susceptible isolates to any beta-lactam agent, the MIC_{90} of moxifloxacin was fourfold higher than that for the susceptible isolates. No theoretical link has been proposed between penicillin and fluoroquinolone susceptibility, and the known mechanisms of resistance to the two drugs are quite different.

There have been numerous changes in the nomenclature and taxonomy of the *Streptococcus* genus, mainly in the non beta-hemolytic species (9). Nevertheless, viridans streptococci can be identified on the basis of typical phenotypic characteristics (9). With the system we use to classify streptococci, most individual species cannot be identified but are placed in one of the five groups (9, 32, 33). We think that the grouping used was useful to show the different behavior of streptococci against the antimicrobials tested. Nevertheless, in the future it would be desirable in molecular genetic procedures to use a universal language when dealing with non beta-hemolytic streptococci.

In conclusion, most of the streptococci isolated from the bloodstream after dental extractions were susceptible *in vitro* to beta-lactam agents. The high percentage of streptococci resistant to erythromycin and clindamycin could restrict their usefulness as prophylactic drugs. Currently, there are no NCCLS interpretative criteria standards with respect to the efficacy of moxifloxacin against streptococci other than *Streptococcus pneumoniae*. However, all the isolates showed *in vitro* a low MIC to moxifloxacin, making this a promising antimicrobial alternative for the prevention of streptococcal focal infections associated with certain dental manipulations, when the administration of beta-lactam agents is not indicated.

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