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Comparative in-vitro activities of moxifloxacin, trovafloxacin, quinupristin/dalfopristin and linezolid against staphylococci

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The antistaphylococcal activities of four newly developed antibiotics, moxifloxacin (an 8-methoxyfluoroquinolone), trovafloxacin (a naphthyridone), quinupristin/dalfopristin (a semi-synthetic streptogramin) and linezolid (an oxazolidinone), were examined and compared with those of ciprofloxacin, vancomycin and teicoplanin, using an agar dilution method. A total of 245 clinical isolates of staphylococci, including a large number of clonally different methicillin-resistant strains, were tested. The new agents tested exhibited wide-spectrum antistaphylococcal activity against both methicillin-susceptible and methicillin-resistant strains. In contrast to the quinolones, the in-vitro activities of quinupristin/dalfopristin, linezolid and the glycopeptides remained almost unchanged, irrespective of the resistance phenotype for methicillin. A number of isolates with elevated quinolone MICs were observed.

Introduction

The incidence of infections caused by multiresistant Gram-positive bacteria is increasing despite advances in antibacterial therapy over the last two decades. Thus, there continues to be a need for highly active antimicrobial agents, especially for therapy of infections caused by methicillin-resistant staphylococci.

Moxifloxacin, a newly developed 8-methoxyfluoroquinolone, and trovafloxacin, a new fluoronaphthyridone derivative, were reported to be effective against Gram-positive bacteria.[1,2] Similarly, quinupristin/dalfopristin (in a ratio of 30:70), the first semisynthetic injectable pristinamycin, and linezolid, a novel oxazolidinone, have potent activity against a variety of Gram-positive bacteria.[3,4]

The aims of this study were (i) to evaluate the in-vitro activity of moxifloxacin, trovafloxacin, quinupristin/dalfopristin, and linezolid against a large number of different and well-characterized staphylococcal strains, particularly against clonally different methicillin-resistant strains isolated from several geographic locations in Germany, and (ii) to compare the in-vitro antistaphylococcal activities of the newly developed antimicrobial agents with compounds such as ciprofloxacin, vancomycin and teicoplanin.

Materials and methods

A total of 245 staphylococci freshly isolated from clinical material were tested. These isolates came from 14 university and community hospitals in different parts of Germany. Only one isolate per patient was tested. Multiple isolates of the same strain were initially excluded by antibiograms and phenotypic characterization. In addition, because methicillin-resistant *Staphylococcus aureus* strains may cause outbreaks, we used several other criteria to avoid including multiple isolates of the same strain: firstly, isolates were collected over a period of years, which would make collection of a single clone unlikely. Secondly, isolates were collected from different geographic locations in Germany, which would also reduce the chance of obtaining a single clone. Finally, when isolates with similar antibiograms and phenotypes were obtained, we performed pulsed-field gel electrophoresis and selected only one example of each strain.

The 104 *S. aureus* strains included 17 penicillin-susceptible (PSSA), 27 methicillin-susceptible (MSSA) and 60 methicillin-resistant (MRSA) strains. The 141 coagulase-negative staphylococci (CoNS) comprised 20 methicillin-susceptible *Staphylococcus epidermidis* (MSSE), 29 methicillin-resistant *S. epidermidis* (MRSE), 16 methicillin-susceptible *Staphylococcus haemolyticus* (MSSH), 43

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methicillin-resistant *S. haemolyticus* (MRSH) and 33 other coagulase-negative staphylococci belonging to the following species: nine *Staphylococcus hominis*, eight *Staphylococcus lugdunensis*, four *Staphylococcus warneri*, four *Staphylococcus capitis*, two *Staphylococcus schleiferi*, two *Staphylococcus simulans*, two *Staphylococcus caprae*, one *Staphylococcus saprophyticus* and one *Staphylococcus sciuri*. The staphylococci were identified from a variety of conventional phenotypic characteristics and by using the API-Staph system (ATB32 Staph, BioMérieux, Marcy-l'Etoile, France). Erythromycin-resistant and clindamycin-resistant strains were included. The MICs were determined on Mueller–Hinton agar (Difco, Augsburg, Germany), using an agar dilution technique with an inoculum of 10^5 cfu. Isolates were confirmed to be methicillin resistant by supplementing the agar with 2% NaCl (read after incubation for 48 h at 30°C), as well as by detection of the *mecA* gene in strains with non-definable resistance phenotypes. The following antimicrobial agents were used and obtained from their respective manufacturers: moxifloxacin and ciprofloxacin (both supplied by Bayer AG, Leverkusen, Germany), trovafloxacin (Pfizer Central Research, Groton, CT, USA), linezolid (Pharmacia & Upjohn Co., Kalamazoo, MI, USA), quinupristin/dalfopristin (Rhône-Poulenc Rorer R-D, Vitry-sur-Seine, France), vancomycin (Eli Lilly & Co., Indianapolis, IN, USA), teicoplanin (Hoechst Marion Roussel Deutschland GmbH, Frankfurt, Germany). The quinolones were tested in concentrations in the range 0.031–128 mg/L; quinupristin/dalfopristin, linezolid and the glycopeptides were tested in concentrations in the range 0.031–8 mg/L. The results were read after 18 h incubation at 36°C. The following reference strains were included as controls: *S. aureus* ATCC 25923; ATCC 29213; ATCC 43300; *Escherichia coli* ATCC 35218; *Pseudomonas aeruginosa* ATCC 27853. Additionally, sterility and growth controls were always performed.

Results

The MIC ranges, MIC_{50} values and MIC_{90} values for the 104 strains of *S. aureus* are shown in Table I. In comparison with the other agents tested, moxifloxacin and trovafloxacin had the highest in-vitro activity against PSSA and MSSA (MIC_{90} ≤0.063 mg/L). Against these strains, quinupristin/dalfopristin and ciprofloxacin were at least eight-fold less active than moxifloxacin or trovafloxacin, although they were slightly more active than linezolid or the glycopeptides tested. The in-vitro activities of the newly developed agents against MRSA were similar to those of the glycopeptides, with quinupristin/dalfopristin and vancomycin being more active than the other compounds.

Table I. In-vitro activity against *S. aureus*

		MIC (mg/L)		
S. aureus	Agent	range	MIC_{50}	MIC_{90}
PSSA	moxifloxacin	≤0.031–0.063	≤0.031	0.063
(n = 17)[a]	trovafloxacin	≤0.031–0.063	≤0.031	≤0.031
	ciprofloxacin	0.125–1	0.25	0.5
	quinupristin/dalfopristin	0.25–0.5	0.5	0.5
	linezolid	1–2	2	2
	teicoplanin	0.25–1	0.5	1
	vancomycin	0.5–2	1	1
MSSA	moxifloxacin	≤0.031–4	≤0.031	0.063
(n = 27)	trovafloxacin	≤0.031–8	≤0.031	0.063
	ciprofloxacin	0.125–64	0.5	0.5
	quinupristin/dalfopristin	0.25–1	0.5	0.5
	linezolid	2–4	2	2
	teicoplanin	0.5–1	0.5	1
	vancomycin	0.5–1	1	1
MRSA	moxifloxacin	≤0.031–8	1	2
(n = 60)	trovafloxacin	≤0.031–8	0.5	4
	ciprofloxacin	≤0.031–>128	16	64
	quinupristin/dalfopristin	≤0.031–2	1	1
	linezolid	≤0.031–2	2	2
	teicoplanin	≤0.031–4	1	2
	vancomycin	≤0.031–2	1	1

[a] n = Number of strains tested.

The antistaphylococcal activities of vancomycin, teicoplanin, quinupristin/dalfopristin and linezolid remained almost unchanged, irrespective of the methicillin resistance phenotype. Although single *S. aureus* isolates with elevated MICs (8 mg/L) of moxifloxacin (one isolate) and trovafloxacin (six isolates) were observed, all isolates were inhibited by ⩽2 mg/L of quinupristin/dalfopristin or vancomycin. Ciprofloxacin showed poor activity against MRSA, with MICs up to ⩾128 mg/L. According to the MIC_{90} values, moxifloxacin was 32-fold more active than ciprofloxacin against MRSA.

The MIC ranges, MIC_{50}s and MIC_{90}s for the 141 CoNS are shown in Table II. Quinupristin/dalfopristin was the most active antimicrobial agent against all *S. epidermidis* strains and against MRSH strains. Of the quinolones, moxifloxacin and trovafloxacin had similar in-vitro activities against CoNS, with moxifloxacin being slightly more active against methicillin-resistant strains. By comparison, moxifloxacin was up to 32-fold more active than ciprofloxacin, especially against the methicillin-resistant strains. However, single isolates of *S. epidermidis* and particularly of *S. haemolyticus* with elevated MICs of moxifloxacin (six isolates) and trovafloxacin (13 isolates) were observed (MIC 8 and 16 mg/L, respectively). All methicillin-suscep-

Table II. In-vitro activity against coagulase-negative staphylococci

CoNS	Agent	MIC (mg/L) range	MIC_{50}	MIC_{90}
MSSE	moxifloxacin	⩽0.031–8	⩽0.031	1
(n = 20)[a]	trovafloxacin	⩽0.031–8	⩽0.031	1
	ciprofloxacin	⩽0.031–16	0.125	16
	quinupristin/dalfopristin	0.25–0.5	0.25	0.25
	linezolid	0.5–1	1	1
	teicoplanin	0.5–2	1	2
	vancomycin	0.5–2	1	1
MRSE	moxifloxacin	⩽0.031–4	0.5	2
(n = 29)	trovafloxacin	⩽0.031–8	1	4
	ciprofloxacin	0.063–>128	4	64
	quinupristin/dalfopristin	0.25–0.5	0.5	0.5
	linezolid	1–2	1	2
	teicoplanin	0.5–>8	1	4
	vancomycin	1–2	2	2
MSSH	moxifloxacin	⩽0.031–1	⩽0.031	0.063
(n = 16)	trovafloxacin	⩽0.031–1	⩽0.031	⩽0.031
	ciprofloxacin	⩽0.031–8	0.125	0.5
	quinupristin/dalfopristin	⩽0.031–0.5	0.5	0.5
	linezolid	0.5–1	1	1
	teicoplanin	0.5–8	2	4
	vancomycin	⩽0.031–2	1	2
MRSH	moxifloxacin	⩽0.031–8	1	8
(n = 43)	trovafloxacin	⩽0.031–16	2	8
	ciprofloxacin	0.125–>128	16	128
	quinupristin/dalfopristin	0.25–2	0.5	1
	linezolid	0.5–1	1	1
	teicoplanin	2–>8	4	>8
	vancomycin	1–4	1	2
CoNS	moxifloxacin	⩽0.031–0.25	0.063	0.125
(others)	trovafloxacin	⩽0.031–0.125	⩽0.031	0.063
(n = 33)	ciprofloxacin	0.063–0.5	0.125	0.25
	quinupristin/dalfopristin	0.125–2	0.25	1
	linezolid	0.25–2	1	1
	teicoplanin	0.125–8	0.5	2
	vancomycin	0.5–2	1	1

[a] n = Number of strains tested.

tible and methicillin-resistant CoNS were inhibited by ≤2 mg/L of quinupristin/dalfopristin, linezolid and (apart from two MRSH strains) vancomycin. From comparison of the MIC_{90} values, vancomycin was at least two-fold more active than teicoplanin against all CoNS tested. With regard to methicillin-resistant *S. haemolyticus*, vancomycin showed at least four-fold more activity than moxifloxacin (MIC_{90} 8 mg/L) or teicoplanin (MIC_{90} >8 mg/L).

The in-vitro activities of the antimicrobial agents tested remained almost unchanged, irrespective of the resistance phenotype for erythromycin and/or clindamycin. Quality control of all MIC determinations was performed using the reference strains mentioned above. The MICs for these strains were within acceptable limits throughout testing; e.g. for *S. aureus* ATCC 25923 the MICs were: moxifloxacin, 0.06 mg/L; trovafloxacin, ≤0.031 mg/L; ciprofloxacin, 1 mg/L; quinupristin/dalfopristin, 1 mg/L; linezolid, 2 mg/L; teicoplanin, 1 mg/L and vancomycin, 1 mg/L.

Discussion

In recent years the incidence of multi-drug-resistant Gram-positive cocci has increased dramatically worldwide. *S. aureus* and CoNS show a remarkable propensity for resistance to various antibiotics.[5] As a result of the high degree of multiple resistance in these pathogens, treatment options are very limited and glycopeptides are often the only drugs still effective. However, glycopeptide resistance has been reported in CoNS and recently *S. aureus* strains with reduced susceptibility to vancomycin were isolated in Japan, the USA and Europe.[6] Thus, alternatives to these antimicrobials are urgently needed, not only for the treatment of infections caused by multi-resistant strains, but also to reduce the increasing selection pressure from glycopeptides on Gram-positive pathogens in hospitals. In this context, the ability of the newly developed quinolones moxifloxacin and trovafloxacin and especially of the streptogramin quinupristin/dalfopristin and the oxazolidinone linezolid to inhibit MRSA may be of major clinical importance. The in-vitro activities of these agents were similar to or even higher than those of teicoplanin and vancomycin against *S. aureus*, including methicillin-resistant strains and, apart from methicillin-resistant *S. haemolyticus* strains, also against all other CoNS tested. Against MRSH, quinupristin/dalfopristin and linezolid showed slightly higher activities than vancomycin or teicoplanin; the new fluoroquinolones were less active.

The antimicrobial susceptibilities of our staphylococci were generally in agreement with those reported by other investigators, indicating that the newly developed agents tested appear promising for treatment of multi-resistant Gram-positive organisms.[1–4] However, in contrast to previous studies, we observed a larger number of strains with elevated MICs, particularly of the quinolones, resulting in MIC_{90} values up to 16-fold higher than reported by other investigators.[2,3,7–9] This finding might be explained by the fact that in most of the aforementioned studies, only a limited number of different staphylococcal species, especially of methicillin-resistant strains, were studied and multiple isolates of the same strain were not excluded by phenotypic or genomic typing,[1–4,8] which is particularly important for MRSA, which often cause at least regional outbreaks with the same strain.[10]

In summary, our data indicate that the newly developed agents tested exhibit sufficient antistaphylococcal activity against both methicillin-susceptible and methicillin-resistant strains, stimulating further evaluation of these agents for therapy of infections caused by multi-resistant staphylococci. However, single strains of *S. aureus, S. epidermidis* and *S. haemolyticus* with elevated MICs of moxifloxacin or trovafloxacin may be found.

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