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Resistance Patterns of Methicillin- and Mupirocin-resistant *S. aureus* from Uncomplicated Skin and Skin Structure Infections (SSSIs) in the United States from March 2004–March 2005; Retapamulin Surveillance Study

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Abstract

Background: Retapamulin is a novel semi-synthetic pleuromutilin currently in development as a topical antimicrobial for the treatment of skin and skin structure infections (SSSIs). The mode of action for pleuromutilin is unique and shows no cross-resistance to other classes of antibiotics and is fully active against skin bacterial isolates carrying resistance determinants to established agents including β-lactams, macrolides, quinolones, fusidic acid and mupirocin. **Methods:** Clinical isolates of *Staphylococcus aureus* were collected from 9 sites in the United States during 2004 and 2005. All isolates were sent to the central laboratory for testing, identification confirmation and confirmation of oxacillin resistance. Organisms were frozen at -70°C prior to evaluation. Susceptibility testing was performed using broth microdilution panels. Quality controls were performed each day of testing following Clinical and Laboratory Standards Institute (CLSI; formerly the National Committee for Clinical Laboratory Standards [NCCLS]) guidelines. **Results:** A total of 994 *S. aureus* isolates were collected of which 416 or 41.9% were determined to be methicillin-resistant (MRSA). Mupirocin-resistance (MURMRSA) was detected in 61/416 or 14.7% of all MRSAs. Retapamulin MIC_{90}s against MRSA/MURMRSA isolates is 0.12/0.12 µg/mL. The same isolates exhibited MIC_{90}s (expressed in µg/mL) of >64/>64 for neomycin; 0.5/1 for fusidic acid; >128/>128 for bacitracin; >32/>32 for erythromycin; 32/32 for tetracycline; 2/2 for linezolid; 32/32 for cephalothin; 4/8 for gentamicin; and 16/16 for amoxicillin/clavulanic acid. **Conclusions:** Retapamulin demonstrated greater activity against methicillin- and mupirocin-resistant *S. aureus* isolates than current commonly used topical and oral antimicrobial agents in the treatment of uncomplicated SSSIs.

Introduction

Retapamulin (SB-275833; Figure 1), a novel derivative of the pleuromutilin class of antimicrobials, is currently in development for the topical treatment of a variety of Gram positive pathogens associated with secondarily infected traumatic lesions and dermatoses. The pleuromutilins are potent inhibitors of protein synthesis in bacteria through the interference of peptide bond formation by binding to the peptidyl transferase center of the 50S ribosomal subunit.[1] Due to the unique pleuromutilin mode of action, retapamulin shows no target specific cross-resistance to other classes of antibacterials.

Mupirocin is a topical antimicrobial commonly used in the treatment of uncomplicated skin infections and also nasal decolonization of methicillin-resistant *Staphylococcus aureus* (MRSA). Mupirocin activity against MRSA has decreased since the advent of mupirocin-resistant *S. aureus* and is linked to increased usage and exposure to the drug.[2,3] Due to a rise in drug resistance and the potential for reduced effectiveness of existing treatments, there is an increased need for new antibiotics with activity against drug-resistant organisms. This study looked at the *in vitro* activity of retapamulin against a geographically diverse population of MRSA and mupirocin-resistant *S. aureus* from uncomplicated skin and skin structure infections (SSSI) in the USA.

Materials and Methods

- MIC endpoints were determined by broth microdilution and interpreted according to Clinical and Laboratory Standards Institute (CLSI, formerly the National Committee for Clinical Laboratory Standards [NCCLS]) guidelines[4] for retapamulin and 14 comparators in dried broth microdilution panels (Trek Diagnostic Systems Ltd, West Sussex, UK). Comparator antimicrobial agents included: amoxicillin-clavulanic acid, bacitracin, ceftriaxone, cephalothin, clindamycin, cloxacillin, erythromycin, fusidic acid, gentamicin, linezolid, mupirocin, neomycin, penicillin, and tetracycline.
- All study organisms were clinical isolates collected and frozen at -70°C from March 2004 to March 2005 from 9 sites in the USA. All isolates were obtained from uncomplicated SSSI, primarily from infections seen in community settings. Isolates were obtained from both adult and pediatric patients with one isolate per patient.
- Organism collection, transport, confirmation of organism identification, antimicrobial susceptibility testing, as well as construction and management of a centralized database, were coordinated by International Health Management Associates, Inc. (IHMA, Schaumburg, IL, USA).
- A total of 994 *S. aureus* isolates were collected from patients in hospital and community settings and tested. Of these, 416 (41.9%) were methicillin-resistant, 103 (10.4%) were mupirocin-resistant and 61 (6.1%) were methicillin- and mupirocin-resistant. These rates may be somewhat higher than those observed in routine clinical practice as surveillance studies only reflect data from patients for whom a culture and susceptibility testing were performed.
- Mueller-Hinton broth (Sensititre®, Cleveland, OH, USA) was used for all *Staphylococcus* species.
- The trays were incubated at 35°C in ambient air for 16–20 h before reading the MIC endpoints.
- Quality control testing was performed each day of testing as specified by the CLSI using the following isolates: *S. aureus* ATCC 29213 and *S. aureus* ATCC 25923. In addition, quality control ranges previously determined for retapamulin were used as a control.[5]
- The total number of isolates, MIC_{50} (µg/mL), MIC_{90} (µg/mL) and MIC ranges were determined for all antimicrobial agents tested. Interpretive criteria and resistant phenotypes to the corresponding antimicrobial agent were defined according to CLSI breakpoints[6] or the literature (mupirocin[7] and fusidic acid[8] only). Methicillin-resistance was based upon oxacillin screening agar.

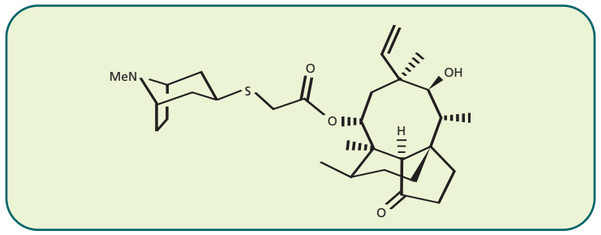


Figure 1. Chemical Structure of Retapamulin

Results

The activity of retapamulin and comparator antimicrobials is presented in Tables 1 and 2 and Figures 2–4.

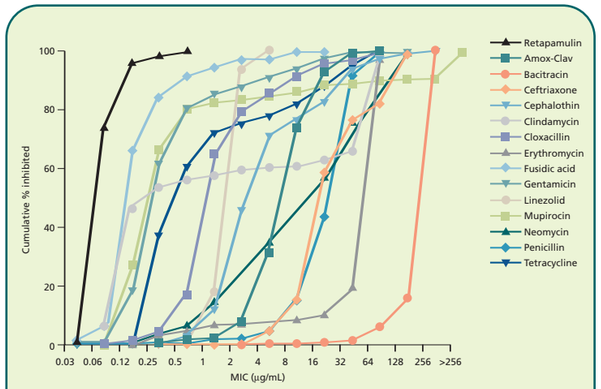
Conclusions

- Retapamulin demonstrated excellent *in vitro* activity against methicillin-resistant, mupirocin-resistant, and mupirocin-resistant/methicillin-resistant *S. aureus* isolates from uncomplicated SSSIs, with MIC_{90} values at least 8-fold lower than those of any comparator in this study including linezolid, mupirocin, and fusidic acid.
- Against all 994 *S. aureus* isolates tested, retapamulin was the most potent agent *in vitro* and inhibited all *S. aureus* isolates at a MIC of ≤0.5 µg/mL, including methicillin-resistant, mupirocin-resistant, and mupirocin-resistant/methicillin-resistant isolates.
- Retapamulin's retention of potent *in vitro* activity against *S. aureus* strains resistant to one or more of the agents commonly used in the treatment of SSSIs could potentially provide a useful option for treatment of such infections.
- Clinical trial data is needed to assess the clinical significance of these *in vitro* findings.

Table 1. MIC (µg/mL) Summary for Retapamulin Activity against 994 *S. aureus* Isolates Recovered from SSSIs

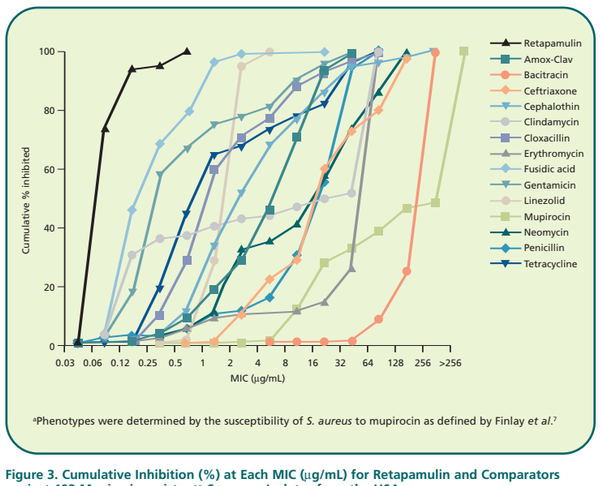
Phenotype[a,b] (n)	MIC (µg/mL)		
	Range	MIC_{50}	MIC_{90}
All *S. aureus* (994)	0.015–0.5	0.06	0.12
Methicillin-susceptible (578)	0.015–0.5	0.06	0.12
Methicillin-resistant (416)	0.03–0.5	0.06	0.12
Mupirocin-susceptible (891)	0.015–0.5	0.06	0.12
Mupirocin-resistant (103)	0.03–0.5	0.06	0.12
Mupirocin-resistant and methicillin-susceptible (42)	0.03–0.5	0.06	0.12
Mupirocin-resistant and methicillin-resistant (61)	0.03–0.25	0.06	0.12

[a]Phenotypes were determined by the *in vitro* susceptibility of the respective antimicrobial agent against the corresponding organism as defined in CLSI document M100-S15 unless otherwise noted;[6] methicillin = oxacillin activity.
[b]Mupirocin susceptibility breakpoints (≤4 µg/mL susceptible; ≥8 µg/mL resistant) as defined by Finlay *et al.*[7]



[a]Phenotypes were determined by the susceptibility of *S. aureus* to oxacillin as defined in CLSI document M100-S15.[6]

Figure 2. Cumulative Inhibition (%) at Each MIC (µg/mL) for Retapamulin and Comparators against 416 Methicillin-resistant[a] *S. aureus* Isolates from the USA



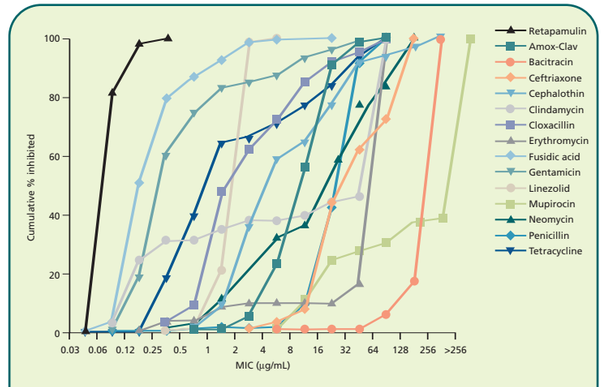
[a]Phenotypes were determined by the susceptibility of *S. aureus* to mupirocin as defined by Finlay *et al.*[7]

Figure 3. Cumulative Inhibition (%) at Each MIC (µg/mL) for Retapamulin and Comparators against 103 Mupirocin-resistant[a] *S. aureus* Isolates from the USA

Table 2. MIC (µg/mL) Summary for Retapamulin and Comparators against S. *aureus* Isolates by Resistant Phenotype

Compound[c]	MRSA[a] (n = 416)		Mupirocin-resistant[b] *S. aureus* (n = 103)		Mupirocin[b]- and methicillin-resistant[a] *S. aureus* (n = 61)	
	%Res	MIC_{90}	%Res	MIC_{90}	%Res	MIC_{90}
Retapamulin	NA	0.12	NA	0.12	NA	0.12
Amox-Clav[d]	100	16	68	16	100	16
Bacitracin	NA	>128	NA	>128	NA	>128
Ceftriaxone	100	>64	64.1	>64	100	>64
Cephalothin	100	32	60.2	32	100	32
Clindamycin	40.6	>32	57.3	>32	62.3	>32
Cloxacillin	NA	8	NA	16	NA	16
Erythromycin	92.8	>32	89.3	>32	90.2	>32
Fusidic acid	3.6	0.5	1	1	1.6	1
Gentamicin	6.3	4	9.7	8	6.6	8
Linezolid	0	2	0	2	0	2
Methicillin	100	NA	59.2	NA	100	NA
Mupirocin	14.7	128	100	>256	100	>256
Neomycin	NA	>64	NA	>64	NA	>64
Penicillin	100	32	97.1	32	100	32
Tetracycline	18.3	32	22.3	32	23	32

[a]Phenotype was determined by the susceptibility of *S. aureus* to oxacillin as defined in CLSI document M100-S15.[6]
[b]Phenotype was determined by the susceptibility of *S. aureus* to mupirocin as defined by Finlay *et al.*[7]
[c]Interpretive criteria of compounds defined in CLSI document M100-S15 where available; mupirocin susceptibility (≤4 µg/mL susceptible; ≥8 µg/mL resistant) defined in Finlay *et al.*;[7] fusidic acid susceptibility (≤1 µg/mL susceptible; ≥4 µg/mL resistant) defined in Toma and Barriault;[8] Note: β-lactams reported as resistant for MRSA in accordance with current CLSI guidelines.
[d]Amoxicillin/clavulanic acid was tested in a 2:1 ratio; MICs are reported based on the amoxicillin concentration.
Res, resistant; NA, not available.



[a]Phenotypes were determined by the susceptibility of *S. aureus* to oxacillin as defined in the CLSI document M100-S15,[6] and mupirocin as defined by Finlay *et al.*[7]

Figure 4. Cumulative Inhibition (%) at Each MIC (µg/mL) for Retapamulin and Comparators against 61 Mupirocin-resistant/Methicillin-resistant[a] *S. aureus* Isolates from the USA

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Acknowledgements

This study was sponsored by a grant from GlaxoSmithKline Pharmaceuticals.