

In Vitro Activity of Retapamulin against *Staphylococcus aureus* and *Streptococcus pyogenes* Isolated from Skin and Skin Structure Infections

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Abstract

Background: Retapamulin (RP) is a semisynthetic pleuromutilin, 50S protein synthesis inhibitor (PSI) approved in 2007 for the topical treatment of impetigo in the USA and uncomplicated skin infections and impetigo in Europe caused by methicillin-susceptible *Staphylococcus aureus* (MSSA) and *Streptococcus pyogenes* (SP).
Methods: The *in vitro* activities of RP and 14 comparators were assessed by CLSI broth microdilution against 986 MSSA and 254 SP isolates prospectively collected from adult and pediatric patients with skin and skin structure infections in 25 sites in Belgium, France, Germany, Italy, Spain, and the UK between October 2008 and December 2009.
Results: The *in vitro* activity of RP against MSSA with different resistance (R) phenotypes and SP was:

Species	Phenotype (n)	RP MIC (µg/ml)			% S*	
		50%	90%	Range		
MSSA	All (986)	0.12	0.12	0.004-4	99.8	
	Gentamicin-R (41)	0.12	0.25	0.06-0.25	100	
	Tetracycline-R (64)	0.12	0.12	0.03-0.5	100	
	Erythromycin-R (180)	0.12	0.12	0.03-0.5	100	
	Clindamycin-R (38)	0.12	0.12	0.03-0.25	100	
	Linezolid-R (20)	0.12	0.25	0.06-0.5	100	
	Mupirocin High-Level R (20)	0.12	0.12	0.06-0.25	100	
	Fusidic Acid-R (103)	0.12	0.12	0.06-0.5	100	
	<i>S. pyogenes</i>	All (254)	0.03	0.06	0.008-0.12	100

*Susceptible microbiological cutoffs for RP: SA ≤0.5 µg/ml; SP ≤0.25 µg/ml (from Antimicrob. Agents Chemother. 2008;52:3863-7).
Against MSSA, all topical agents tested [MIC₉₀s (µg/ml): bacitracin 128; erythromycin >32; fusidic acid 4; clindamycin 0.25; mupirocin, 0.5] exhibited equal or higher MIC₉₀s than RP (0.12 µg/ml).

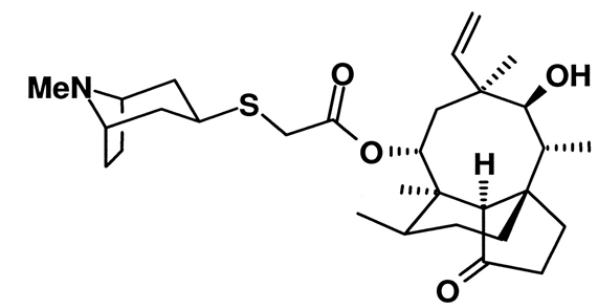
Conclusions: RP was highly active *in vitro* against MSSA resistant to other PSIs and all SP.

Introduction

Retapamulin is a semisynthetic pleuromutilin that was approved in 2007 in the United States for the topical treatment of impetigo caused by methicillin-susceptible *Staphylococcus aureus* (MSSA) and *Streptococcus pyogenes* and in Europe for the treatment of uncomplicated skin infections and impetigo caused by methicillin-susceptible *S. aureus* and *S. pyogenes*. Retapamulin is emerging as an important topical antibacterial agent as resistance increases to older, more frequently prescribed topical antibacterial agents such as mupirocin and fusidic acid (1).

Pleuromutilins, first isolated from *Pleurotus mutilus* (an edible mushroom), inhibit protein synthesis in susceptible bacteria by binding to the peptidyl transferase center of the 50S ribosomal subunit; ribosomal protein L3 has been demonstrated to be important for retapamulin binding (1). Pleuromutilin binding to the 50S ribosomal subunit is distinct from the binding of other protein synthesis inhibitors and to cross-resistance to other classes of antibacterial agents has been rarely reported.

The current study determined the *in vitro* activities of retapamulin and relevant comparators against a geographically diverse collection of methicillin-susceptible *S. aureus* and *S. pyogenes* from skin and skin structure infections. The chemical structure of retapamulin is shown below:



Methods

- The *in vitro* activities of retapamulin and 14 comparative agents were evaluated against 986 methicillin-susceptible *S. aureus* and 254 *S. pyogenes* isolated from patients with skin and skin structure infections from selected centers in 6 countries in Europe (Belgium, France, Germany, Italy, Spain, United Kingdom); the isolates were collected consecutively between October 2008 and December 2009 from both pediatric and adult patients (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).
- Custom dried broth microdilution panels were supplied by TREK (TREK Diagnostic Systems, Cleveland, OH). The dilution ranges (µg/ml) for each antimicrobial agent were: mupirocin (0.015-512), retapamulin (0.002-256), clindamycin (0.015-32), erythromycin (0.015-32), fusidic acid (0.015-32), gentamicin (0.03-64), penicillin (0.015-32), neomycin (0.03-64), bacitracin (0.06-128), tetracycline (0.06-16), ciprofloxacin (0.015-32), linezolid (0.015-16), ceftriaxone (0.015-64), amoxicillin-clavulanic acid (0.015-32, expressed as amoxicillin concentration only, tested as 2:1 ratio of amoxicillin:clavulanic acid), and trimethoprim-sulfamethoxazole (0.015-32, expressed as trimethoprim concentration only, tested as 1:19 ratio of sulfamethoxazole). Mueller Hinton broth (Sensititre®, Cleveland, OH) was used for all *S. aureus* isolates; Mueller Hinton broth was supplemented with 3% laked horse blood for *S. pyogenes*. Minimum inhibitory concentration (MIC) endpoints were determined according to CLSI guidelines [2].
- All *S. aureus* isolates were screened by cefoxitin (30 mcg) disk to determine their initial methicillin phenotype; phenotypes were later confirmed by *mecA* PCR. All erythromycin-resistant and clindamycin-susceptible *S. aureus* isolates were subjected to the 'D-Test' to determine inducible clindamycin resistance [2]. Quality control testing was performed each day of testing as specified by the CLSI. The retapamulin quality control range for *S. aureus* ATCC 29213 was 0.06-0.25 µg/ml [4]. Mupirocin MIC QC ranges of 0.06 to 0.5 µg/ml were used with *S. aureus* ATCC 29213 [2] and ≥256 µg/ml for *S. aureus* ATCC BAA-1708.

Results

Table 1. Activity of retapamulin and 14 comparative agents against 986 isolates of methicillin-susceptible *S. aureus*

Agent	N	%Sus*	%Int	%Res	(µg/ml)		
					MIC ₅₀	MIC ₉₀	Range
Retapamulin	986	99.8	0	0.2	0.12	0.12	0.004 - 4
AmoxClav	986	99.4	0	0.6	1	2	0.06 - 32
Bacitracin	986	NA	NA	NA	64	128	2 - >128
Ceftriaxone	986	97.7	1.7	0.6	4	4	1 - >64
Ciprofloxacin	986	90.0	2.8	7.2	0.5	1	0.06 - >32
Clindamycin**	986	95.0	1.1	3.9	0.12	0.25	≤0.015 - >32
Erythromycin**	986	76.7	5.1	18.3	0.5	>32	0.25 - >32
Fusidic Acid	986	88.4	1.1	10.5	0.25	4	0.06 - >32
Gentamicin	986	95.2	0.6	4.2	0.5	1	≤0.03 - >64
Linezolid	986	98.0	0	2.0	2	4	1 - >16
Mupirocin	986	97.6	0	2.4	0.25	0.5	0.06 - >512
Neomycin	986	NA	NA	NA	0.5	2	≤0.03 - >64
Penicillin	986	19.9	0	80.1	4	32	≤0.015 - >32
Tetracycline	986	92.7	0.8	6.5	0.5	2	0.25 - >16
TrimethSulfa	986	98.0	0	2.0	0.06	0.25	0.03 - >32

* Susceptibilities are defined by CLSI document M100-S10 (2010), where available; retapamulin susceptibility defined in [Traczewski and Brown, 2008]; mupirocin susceptibility defined in [Finlay, 1997]; fusidic acid susceptibility defined in [Toma, 1995]; NA=no breakpoints defined. ** All 144 of MSSA that were erythromycin-resistant and clindamycin-susceptible were D-test-positive.

Table 2. Activity of retapamulin and 14 comparative agents against 254 Isolates of *S. pyogenes*

Drug	N	%Sus*	%Int	%Res	(µg/ml)		
					MIC ₅₀	MIC ₉₀	Range
Retapamulin	254	100	0	0	0.03	0.06	0.008 - 0.12
AmoxClav	254	NA	NA	NA	≤0.015	0.03	≤0.015 - 1
Bacitracin	254	NA	NA	NA	1	1	0.12 - >128
Ceftriaxone	254	99.2	0	0.8	0.03	0.03	≤0.015 - 16
Ciprofloxacin	254	NA	NA	NA	0.5	2	0.25 - >32
Clindamycin	254	95.3	0.4	4.3	0.06	0.12	0.03 - >32
Erythromycin	254	91.3	0	8.7	0.06	0.12	≤0.015 - >32
Fusidic Acid	254	NA	NA	NA	8	8	1 - >32
Gentamicin	254	NA	NA	NA	8	8	0.5 - 32
Linezolid	254	100	0	0	1	1	0.12 - 2
Mupirocin	254	NA	NA	NA	0.12	0.25	0.06 - 1
Neomycin	254	NA	NA	NA	64	64	4 - >64
Penicillin	254	98.8	0	1.2	≤0.015	≤0.015	≤0.015 - 0.5
Tetracycline	254	78.4	0	21.7	0.25	>16	0.12 - >16
TrimethSulfa	254	NA	NA	NA	0.25	>32	0.06 - >32

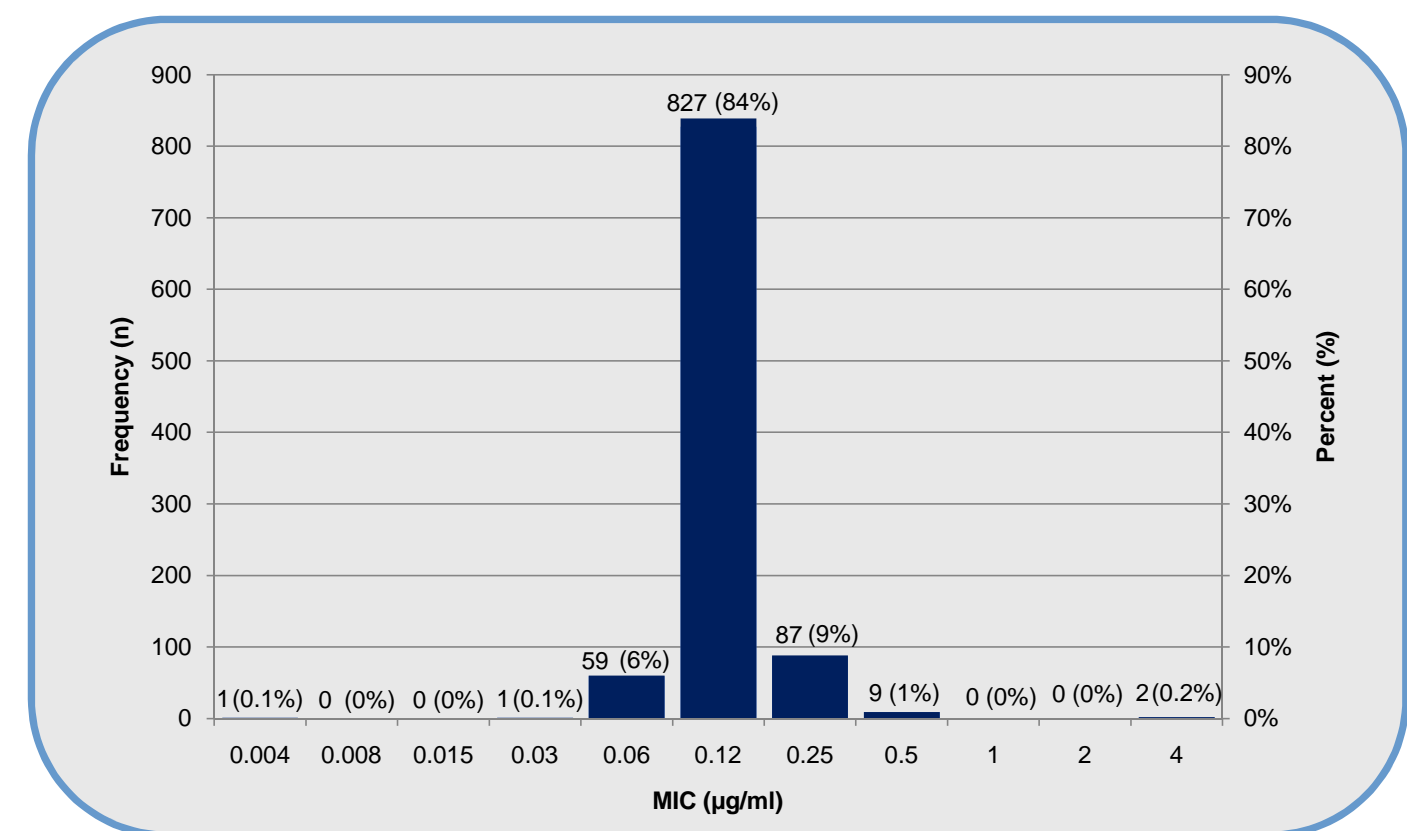
* Susceptibilities are defined by CLSI document M100-S10 (2010), where available; retapamulin susceptibility defined in [Traczewski and Brown, 2008]; NA=no breakpoints defined.

Table 3. Activity of retapamulin against resistant phenotypes of methicillin-susceptible *S. aureus* and *S. pyogenes*

Species	Phenotype (n)	Retapamulin MIC (µg/ml)			% S*
		50%	90%	Range	
MSSA	All (986)	0.12	0.12	0.004-4	99.8
	Gentamicin-R (41)	0.12	0.25	0.06-0.25	100
	Tetracycline-R (64)	0.12	0.12	0.03-0.5	100
	Erythromycin-R (180)	0.12	0.12	0.03-0.5	100
	Clindamycin-R (38)	0.12	0.12	0.03-0.25	100
	Linezolid-R (20)	0.12	0.25	0.06-0.5	100
	Mupirocin High-Level R (20)	0.12	0.12	0.06-0.25	100
	Fusidic Acid-R (103)	0.12	0.12	0.06-0.5	100
	Ciprofloxacin-R (71)	0.12	0.12	0.06-0.5	100
	Penicillin-R (790)	0.12	0.25	0.004-4	99.7
	TrimethSulfa-R (20)	0.12	0.12	0.06-0.25	100
	Isolates R to ≥3 agents (89)	0.12	0.12	0.03-0.25	100
	Isolates R to ≥5 agents (5)	0.12	0.12	0.12	100
<i>S. pyogenes</i>	All (254)	0.03	0.06	0.008-0.12	100
	Clindamycin-R (11)	0.03	0.03	0.03-0.06	100
	Erythromycin-R (22)	0.03	0.06	0.03-0.06	100
	Tetracycline-R (55)	0.03	0.06	0.008-0.06	100
	Isolates R to ≥3 agents (9)	0.03	0.06	0.03-0.06	100

* Susceptibilities are defined by CLSI document M100-S10 (2010), where available; retapamulin susceptibility defined in [Traczewski and Brown, 2008]; mupirocin susceptibility defined in [Finlay, 1997]; fusidic acid susceptibility defined in [Toma, 1995]; NA=no breakpoints defined.

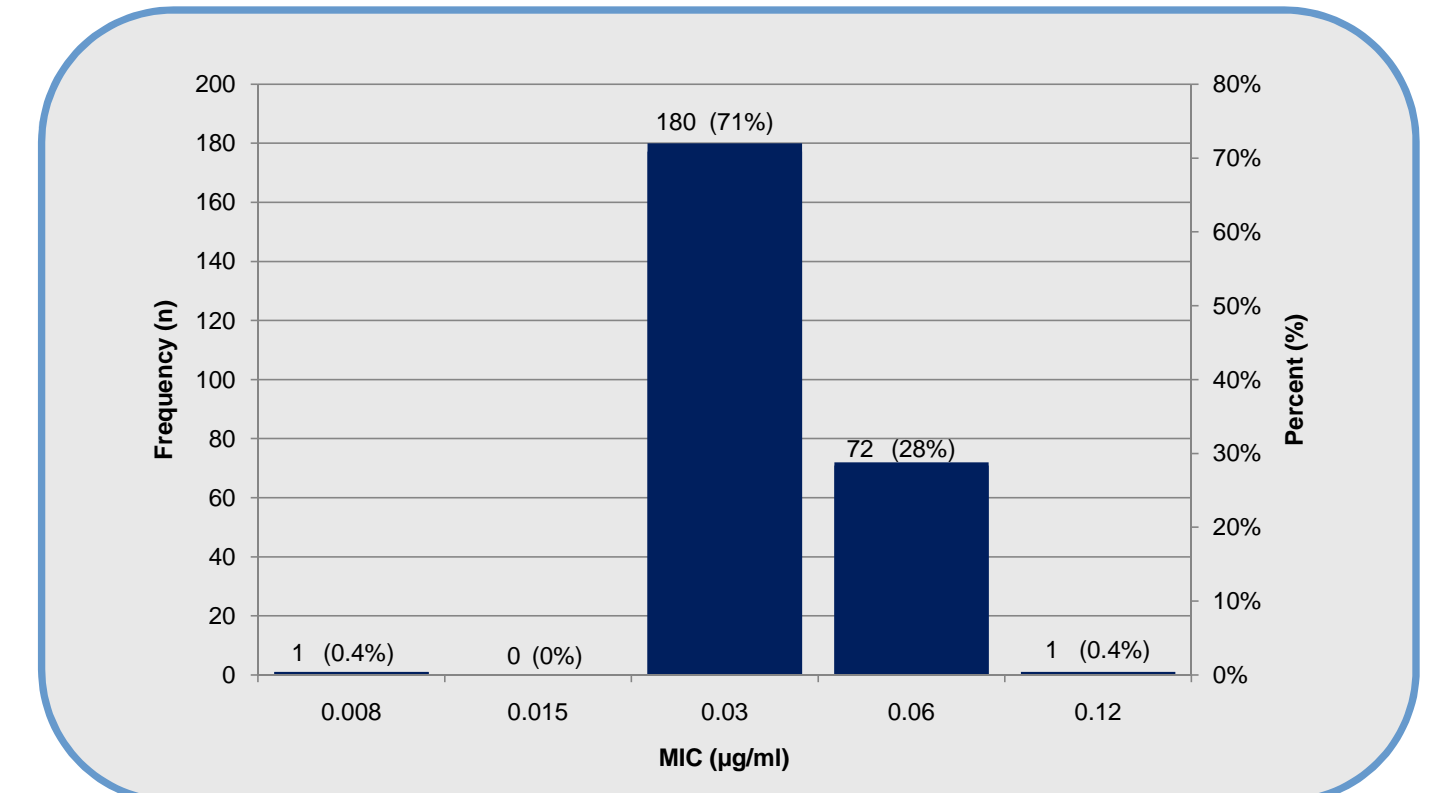
Figure 1. MIC frequency distribution for retapamulin against 986 isolates of methicillin-susceptible *S. aureus*



Acknowledgements

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Figure 2. MIC frequency distribution for retapamulin against 254 isolates of *S. pyogenes*



Conclusions

- Retapamulin was active *in vitro* against recent clinical isolates of methicillin-susceptible *S. aureus* (MIC₉₀, 0.12 µg/ml; Table 1) and *S. pyogenes* (MIC₉₀, 0.06 µg/ml; Table 2) collected from pediatric and adult patients with skin and skin structure infections in six countries in Europe.
- Retapamulin retained *in vitro* activity against isolates of methicillin-susceptible *S. aureus* (MIC₉₀s, 0.12-0.25 µg/ml) and *S. pyogenes* (MIC₉₀s, 0.06 µg/ml) resistant to other protein synthesis inhibitors and against multidrug-resistant isolates (Table 3).
- Retapamulin MICs demonstrated a narrow distribution range with 98.7% (973/986) of isolates of methicillin-susceptible *S. aureus* having MICs of 0.06-0.25 µg/ml (Figure 1) and 99.2% (252/254) isolates of *S. pyogenes* having MICs of 0.03-0.06 µg/ml (Figure 2).

References

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