Activity of Meclocycline Sulfosalicylate Tested Against Oral Pathogens

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AMENDED ABSTRACT

Background: Meclocycline sulfosalicylate (MSS) is a topically-used tetracycline derivative that has been utilized for acne vulgaris treatments and for its other antimicrobial qualities for over three decades. Tetracycline-class agents also have non-antimicrobial features that can minimize the release of free radicals, reduce expression of cytokines and alter degeneration of vascular/connective tissues.

Methods: Over 20 pathogen groups (265 strains) were tested, including 35 staphylococci (15 methicillin-resistant), 10 *E. faecalis*, 80 viridans group streptococci (8 species), 20 ß-haemolytic streptococci, 30 Enterobacteriaceae (3 species), 10 *Pseudomonas aeruginosa*, 10 *Acinetobacters*, 11 *Burkholderia cepacia*, 10 *Moraxella catarrhalis*, 10 *Neisseria* spp., and 27 anaerobic oral flora (10 species). Susceptibility tests were performed by reference CLSI methods (M7-A7, 2006) with associated interpretive criteria (M100-S16, 2006). Comparison tetracyclines (four), tigecycline and six other drugs (data not shown) were used. A MSS breakpoint concentration of ≤4 mg/L was applied for comparisons only, that breakpoint most used for other tetracyclines. Strains with documented *tet*-mechanisms of resistance were also tested.

Results: MSS exhibited equal or greater potency (MIC_{50}) when compared to other tetracyclines against streptococci (0.03-0.25 mg/L), staphylococci (0.06-0.12), *Neisseria* (0.06), most Enterobacteriaceae (1-2 mg/L) and some non-fermentative bacilli (*Acinetobacter* spp., MIC_{50} 0.5 mg/L). *P. aeruginosa* and enterococci were inhibited by MSS with MIC_{90} results at 8-16 mg/L. MSS exhibited cross-resistance with other class agents against strains having *tet* A-E, K-M, O and S mechanisms. Generally, MSS was less potent than minocycline and tigecycline versus resistant mutants.

	MSS MIC (mg/L)		% ≤4 mg/L
Organism (no. tested)	50%	90%	MSS/Tetracycline
Staphylococci (35)	0.12	0.12	100/100
E. faecalis (10)	4	16	50/30
viridans group streptococci (80)	0.06	0.5	96/75
ß-haemolytic streptococci (20)	0.06	2	100/75
Enterobacteriaceae (30)	1	8	80/77
P. aeruginosa (10)	4	8	80/0
Acinetobacter spp. (10)	0.5	4	90/80

Conclusions: At concentrations topically utilized of this non-absorbed tetracycline (MSS), the vast majority of the tested bacteria were inhibited, with lowest MSS MIC values for *S. aureus*, various streptococci and other oral flora (MIC_{90}, ≤2 mg/L).

INTRODUCTION

Meclocycline sulfosalicylate (SS) is a topically applied tetracycline derivative that has been utilized for acne vulgaris treatment and for its other antimicrobial qualities for over three decades. Tetracycline-class agents also have non-antimicrobial features that can minimize the release of free radicals, reduce expression of cytokines and alter degeneration of vascular/connective tissues. To assess the continuing spectrum of meclocycline SS and older peer drugs (doxycycline, minocycline, oxytetracycline and tetracycline HCl), all were tested against a wide variety of contemporary pathogens and upper airway or oral flora. Reference methods were utilized with commonly applied interpretive breakpoints.

MATERIALS AND METHODS

The susceptibility testing methods were reference procedures from the Clinical and Laboratory Standards Institute (CLSI) documents M7-A7 (2006) and M11-A6 (2004). MIC interpretations followed CLSI M100-S16 (2006), where available. For comparison purposes, ≤4 mg/L was the breakpoint for susceptibility applied to all tetracycline derivatives.

Organisms tested (n = 265) were generally recent clinical isolates or index type strains from the American Type Culture Collection (ATCC). These included: *S. aureus* (25; 10 oxacillin-resistant [MRSA]), *S. epidermidis* (10; 5 oxacillin-resistant), *E. faecalis* (10), viridans group streptococci (80; 8 species), *S. pyogenes* (10), serogroups C and G ß-haemolytic streptococci (10), Enterobacteriaceae (30; 3 species), *P. aeruginosa* (10), *A. baumannii* (10), *B. cepacia* (11), *M. catarrhalis* (10), *Neisseria* spp. (10; 5 species) and 27 anaerobic isolates (Tables 1 and 2). Also, a collection of 12 strains of either *S. aureus* or *E. coli* having well characterized tetracycline resistance mechanisms were tested (Table 3).

RESULTS

- Meclocycline SS and minocycline were the most active tetracyclines tested against the staphylococci (MIC_{50}, 0.12 mg/L).
- Only 30.0-80.0% of *E. faecalis* were inhibited at ≤4 mg/L of the tetracyclines, best for doxycycline (MIC_{50}, 4 mg/L).
- Meclocycline SS was markedly superior to other tetracyclines when tested against streptococci by inhibiting 96.3, 100.0 and 100.0% of viridans group streptococci, group A and groups C/G streptococci, respectively (Table 1).
- Essentially all tetracyclines were comparable to tetracycline HCl against Enterobacteriaceae (MIC_{50} ranges, 1-4 mg/L).
- Meclocycline SS had the best activity versus *P. aeruginosa* (80% inhibited at 4 mg/L) and minocycline was most potent (MIC_{90}, 0.5 mg/L) against *A. baumannii*.
- *B. cepacia* was refractory to all tetracyclines, but upper airway colonizers/pathogens such as *M. catarrhalis* and various *Neisseria* spp. were quite susceptible (MIC_{50}, 0.06-0.25

Table 1. Activity of five tetracycline antimicrobial agents tested against 226 recent clinical isolates by reference methods[a].

Organism (no. tested)/ antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible / resistant
S. aureus				
Oxacillin-susceptible (15)				
Meclocycline SS	0.12	0.12	0.06-0.12	100.0 / 0.0
Doxycycline	0.25	0.25	0.12-0.25	100.0 / 0.0
Minocycline	0.12	0.12	0.12-0.25	100.0 / 0.0
Oxytetracycline	0.5	0.5	0.25-0.5	100.0 / 0.0
Tetracycline	0.25	0.5	0.25-0.5	100.0 / 0.0
Oxacillin-resistant (10)				
Meclocycline SS	0.12	0.12	0.06-0.12	100.0 / 0.0
Doxycycline	0.25	0.25	0.12-0.25	100.0 / 0.0
Minocycline	0.12	0.12	0.12-0.25	100.0 / 0.0
Oxytetracycline	0.5	0.5	0.25-1	100.0 / 0.0
Tetracycline	0.5	0.5	0.25-1	100.0 / 0.0
S. epidermidis (10)				
Meclocycline SS	0.12	0.25	0.06-0.25	100.0 / 0.0
Doxycycline	0.5	2	0.25-2	100.0 / 0.0
Minocycline	0.12	0.5	0.12-0.5	100.0 / 0.0
Oxytetracycline	0.5	4	0.5-4	100.0 / 0.0
Tetracycline	0.5	2	0.25-2	100.0 / 0.0
E. faecalis (10)				
Meclocycline SS	4	16	0.06-32	50.0 / 20.0
Doxycycline	4	8	0.12-8	80.0 / 0.0
Minocycline	8	8	0.12->8	40.0 / 10.0
Oxytetracycline	>16	>16	0.25->16	30.0 / 60.0
Tetracycline	>16	>16	0.25->16	30.0 / 70.0
Viridans group streptococci (80)[b]				
Meclocycline SS	0.06	0.5	≤0.002-16	96.3 / 1.3
Doxycycline	0.25	2	≤0.06->8	85.0 / 8.8
Minocycline	0.12	2	≤0.06->8	87.5 / 6.3
Oxytetracycline	0.5	8	≤0.12->16	76.3 / 17.5
Tetracycline	0.5	16	≤0.12->16	76.3 / 21.3
S. pyogenes (10)				
Meclocycline SS	0.03	0.06	0.03-2	100.0 / 0.0
Doxycycline	0.12	0.12	0.12-8	90.0 / 0.0
Minocycline	0.12	0.12	0.12-8	90.0 / 0.0
Oxytetracycline	0.25	0.25	0.25->16	90.0 / 10.0
Tetracycline	0.25	0.25	0.25->16	90.0 / 10.0
ß-haemolytic streptococci other (10)[c]				
Meclocycline SS	0.12	4	0.06-4	100.0 / 0.0
Doxycycline	0.25	8	0.12->8	60.0 / 10.0
Minocycline	0.12	>8	0.12->8	70.0 / 30.0
Oxytetracycline	2	>16	0.25->16	60.0 / 40.0
Tetracycline	4	>16	0.25->16	60.0 / 40.0
E. coli (10)				
Meclocycline SS	1	>64	0.25->64	70.0 / 30.0
Doxycycline	4	>8	1->8	50.0 / 20.0
Minocycline	2	8	0.5-8	70.0 / 0.0
Oxytetracycline	2	>16	1->16	70.0 / 30.0
Tetracycline	4	>16	1->16	70.0 / 30.0
Enterobacter cloacae (10)				
Meclocycline SS	2	4	1-8	90.0 / 0.0
Doxycycline	4	>8	2->8	70.0 / 20.0
Minocycline	4	>8	4->8	70.0 / 20.0
Oxytetracycline	2	16	2-16	80.0 / 20.0
Tetracycline	2	16	2-16	80.0 / 20.0
K. pneumoniae (10)				
Meclocycline SS	1	8	0.5->64	80.0 / 10.0
Doxycycline	2	>8	1->8	80.0 / 20.0
Minocycline	4	>8	1->8	80.0 / 20.0
Oxytetracycline	1	16	1->16	80.0 / 20.0
Tetracycline	2	16	1->16	80.0 / 20.0
P. aeruginosa (10)				
Meclocycline SS	4	8	2-8	80.0 / 0.0
Doxycycline	>8	>8	8->8	0.0 / 90.0
Minocycline	8	>8	4->8	10.0 / 20.0
Oxytetracycline	8	8	4-8	20.0 / 0.0
Tetracycline	16	16	8-16	0.0 / 80.0
A. baumannii (10)				
Meclocycline SS	0.5	4	0.12-32	90.0 / 10.0
Doxycycline	0.12	2	≤0.06-2	100.0 / 0.0
Minocycline	0.12	0.5	≤0.06-2	100.0 / 0.0
Oxytetracycline	2	16	0.5->16	80.0 / 20.0
Tetracycline	1	16	0.5->16	80.0 / 20.0
B. cepacia (11)				
Meclocycline SS	>64	>64	2->64	18.2 / 71.8
Doxycycline	4	>8	0.5->8	54.5 / 45.5
Minocycline	4	>8	0.25->8	63.6 / 27.3
Oxytetracycline	>16	>16	16->16	0.0 / 100.0
Tetracycline	>16	>16	16->16	0.0 / 100.0
M. catarrhalis (10)				
Meclocycline SS	0.06	0.12	0.03-0.12	100.0 / 0.0
Doxycycline	0.12	0.12	≤0.06-0.25	100.0 / 0.0
Minocycline	0.12	0.12	≤0.06-0.12	100.0 / 0.0
Oxytetracycline	0.25	0.5	≤0.12-0.5	100.0 / 0.0
Tetracycline	0.25	0.5	≤0.12-0.5	100.0 / 0.0
Neisseria spp. (10)				
Meclocycline SS	0.06	0.5	0.03-1	100.0 / 0.0
Doxycycline	0.25	1	0.12-1	100.0 / 0.0
Minocycline	0.12	0.5	0.12-1	100.0 / 0.0
Oxytetracycline	0.25	0.5	0.25-2	100.0 / 0.0
Tetracycline	0.25	0.5	0.25-4	100.0 / 0.0

a. Criteria as published by the CLSI [2006], where available. A breakpoint of ≤4 mg/L for susceptibility was applied to all tetracyclines for comparison purposes only.
b. Includes eight different species.
c. Includes serogroups C and G.

- Anaerobes (Table 2) were very susceptible to meclocycline SS with 23 of 27 strains inhibited at ≤0.25 mg/L (Table 2).
- Table 3 shows the variable effects of *tet* resistance mechanisms on the MICs of five tetracyclines and a glycylcycline, tigecycline.

Table 2. MIC population distribution of four tetracyclines tested against 27 anaerobic isolates.

	Occurrences at each MIC (mg/L):												
Antimicrobial Agent	≤0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	≥64
Meclocycline SS	7	2	5	7	2	-	1	-	1	1	-	1	-
Doxycycline	-	-	1	5	9	4	4	1	1	-	-	2	-
Minocycline	1	1	3	10	1	6	1	-	1	1	1	1	-
Tetracycline	NT	NT	2	5	2	14	-	-	-	-	-	3	1

Table 3. Listing of tetracycline and glycylcycline class agent MIC results tested against *S. aureus* (5) and *E. coli* (7) strains with characterized tetracycline resistance mechanisms.

	MIC (mg/L):					
Organism (tet mechanism)	Meclocycline SS	Tetracycline	Doxycycline	Minocycline	Oxytetracycline	Tigecycline
E. coli (A)	>64	>16	8	2	>16	0.12
E. coli (B)	>64	>16	>8	8	>16	0.12
E. coli (C)	>64	>16	>8	4	>16	0.25
E. coli (D)	>64	>16	8	4	>16	0.12
E. coli (E)	>64	>16	>8	2	>16	0.25
E. coli (O)	0.25	1	1	0.5	1	0.06
E. coli (S)	0.25	1	1	0.5	1	0.06
S. aureus (K)	16	>16	2	0.25	>16	0.12
S. aureus (K)	32	>16	2	0.25	>16	0.25
S. aureus (L)	64	>16	8	0.25	>16	0.25
S. aureus (M)	8	>16	8	4	>16	0.12
S. aureus (M)	8	>16	8	8	>16	0.12

CONCLUSIONS

- Compared with currently available tetracycline-class agents at the CLSI breakpoint of ≤4 mg/L, meclocycline SS showed the best activity against staphylococci (MIC_{50}, 0.06-0.12 mg/L), streptococci (MIC_{50}, 0.03-0.25 mg/L), *M. catarrhalis* (MIC_{50}, 0.06 mg/L), anaerobes (MIC_{50}, 0.06 mg/L), and *Neisseria* spp. (MIC_{50}, 0.06 mg/L).
- By testing strains possessing *tet* mechanisms of resistance, many strains considered refractory to the antimicrobial action of other tetracyclines would also be resistant to meclocycline SS.
- Meclocycline SS, among the compared tetracycline derivatives tested, appears to have a balance of potency and breadth of spectrum comparable or superior to drugs in its class, and appears appropriate for use against pathogens associated with oral mucositis by virtue of its anti-inflammatory as well as antimicrobial qualities.

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