Poster #130

In Vitro Antimicrobial Activity of Taurolidine against Isolates Associated with Catheter-Related Bloodstream Infections

Jared L. Crandon, PharmD[1]; Paul R. Rhomberg, BS MT(ASCP)[2]; Mariana Castanheira, PhD[2]; S.J. Ryan Arends, PhD[2]

[1] CorMedix Inc., Berkeley Heights, New Jersey, USA; [2] JMI Laboratories, North Liberty, Iowa, USA

Jared L. Crandon, PharmD
Director, Medical Affairs, CorMedix™
300 Connell Drive, Suite 4200
Berkeley Heights, NJ 07922
jcrandon@cormedix.com

BACKGROUND

- Taurolidine is a novel antimicrobial with broad spectrum antibacterial/antifungal activity and two mechanisms of action that does not lend itself to clinically relevant microbial resistance at concentrations contained within a central venous catheter.
- Taurolidine exerts its activity through damage to microbial cell walls and inhibiting adherence of microorganisms to biological surfaces.
- Taurolidine is a component of a recently FDA-approved catheter lock solution (DefenCath®, taurolidine 13,500 µg/mL and heparin 1000 Units/mL) indicated for reducing the incidence of CRBSI in adult patients receiving chronic hemodialysis through a central venous catheter (HD-CVC).
- Although individual isolates from the clinical program were not available for testing, this study evaluated the in vitro antimicrobial activity of taurolidine against a set of recent clinical isolates representative of those recovered from the LOCK-IT-100 trial and/or commonly associated with CRBSI.

METHODS

LOCK-IT-100 Study Design and Outcomes

- LOCK-IT-100 was a phase 3, randomized, double-blind, active-control, multicenter study aimed to evaluate the efficacy and safety of DefenCath® (taurolidine 13,500mg/L and heparin 1000 units/mL) as a catheter lock solution for the reduction of CRBSI in adult patients receiving chronic hemodialysis.
- Patients randomized 1:1 receive a quantity sufficient to fill each catheter lumen of either taurolidine/heparin or heparin 1000 units/mL following each dialysis session.
- The primary end point was the time to CRBSI defined a one positive blood culture (other than for coagulase-negative staphylococci, which required a confirmatory culture) from either a peripheral site, the catheter hub, or the dialysis blood line, signs and symptoms of infection, and no other apparent source of bloodstream infection.
- Among the 327 patients in the taurolidine/heparin arm and the 326 in the heparin arm, there were 9 and 32 cases of CRBSI, respectively; these equated to a 71% reduction in risk of CRBSI for taurolidine/heparin (Figure 1)
- Table 1 depicts the pathogens recovered from both treatment arms in LOCK-IT-100
- As the actual isolates from LOCK-IT-100 were unavailable, this study includes representative contemporary pathogens.

Taurolidine In Vitro Studies

- 442 bacterial and 50 yeast isolates were selected from the SENTRY Antimicrobial Surveillance Program
- All isolates were collected from the bloodstream of U.S. patients between 2018–2023.
- Challenge isolates were included such as MRSA, MRCoNS, MDR Enterobacterales, MDR Pseudomonas aeruginosa, and MDR Acinetobacter baumannii-calcoaceticus sc.
- Testing followed CLSI broth microdilution guidelines using JMI Laboratories produced susceptibility test panels.
- CAMHB was used for testing bacterial isolates which was supplemented with 2.5–5% LHB for testing Streptococci or 5% OADC when testing MAC isolates.
- RPMI 1640 broth buffered with MOPS and 0.2% (w/v) glucose was used for testing fungal isolates.
- Taurolidine MIC values reported were read at 100% growth inhibition.

ABBREVIATIONS

CAMHB, Cation-adjusted Mueller-Hinton broth
CLSI, Clinical and Laboratory Standards Institute
CRBSI, catheter-related bloodstream infections
LHB, lysed horse blood
MAC, Mycobacterium avium complex
MDR, multidrug-resistant
MOPS, morpholinepropanesulfonic acid
MRCoNS, methicillin-resistant coagulase-negative Staphylococcus
MRSA, methicillin-resistant Staphylococcus aureus
ND, not determined
OADC, oleic acid-albumin-dextrose-catalase
RPMI, Roswell Park Memorial Institute
sc, species complex
VRE, vancomycin-resistant Enterococcus

REFERENCES

CLSI. M07Ed11E. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically. 2018, CLSI: Wayne, PA.
CLSI. M24Ed3E. Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes. 2018, CLSI: Wayne, PA.
CLSI. M24SEd2E. Performance Standards for Susceptibility Testing of Mycobacteria, Nocardia and other Aerobic Actinomycetes. 2023, CLSI: Wayne, PA.
CLSI. M27Ed4. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts. 2017, CLSI: Wayne, PA.
CLSI. M27M44SEd3. Performance Standards for Antifungal Susceptibility Testing of Yeasts. 2022, CLSI: Wayne, PA.
CLSI. M100Ed33E. Performance Standards for Antimicrobial Susceptibility Testing. 2023, CLSI: Wayne, PA.

DISCLOSURES

This study was funded by Cormedix® Inc. Element Iowa City (JMI Laboratories) received compensation for services related to the preparation of this poster.

RESULTS

Table 1. Pathogens recovered from CRBSI during LOCK-IT-100 trial

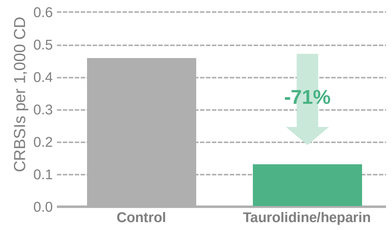
	Taurolidine/ Heparin		Heparin	
Organism	**n**	**%**	**n**	**%**
Total	**9**		**34** [a]	
Gram-Positive	**8**	**88.9%**	**20**	**58.8%**
S. aureus	7	77.8%	8	23.5%
MSSA	*3*	*33.3%*	*3*	*8.8%*
MRSA	*4*	*44.4%*	*5*	*14.7%*
S. epidermidis	1	11.1%	4	11.8%
S. lugdunensis			1	2.9%
S. sanguinis			2	5.9%
S. bovis			1	2.9%
Viridans streptococci			1	2.9%
E. faecalis			3	8.8%
Gram-Negative	**1**	**11.1%**	**14**	**41.2%**
C. korsei			2	5.9%
E. aerogenes			1	2.9%
E. cloacae			4	11.8%
K. pneumoniae	1	11.1%	2	5.9%
S. maltophilia			1	2.9%
S. marcesans			3	8.8%
P. aeruginosa			1	2.9%

[a] Polymicrobial: *P. aeruginosa* and *S. epidermidis*; *S. epidermidis* and Viridans streptococcus

Figure 1. Comparison CRBSI cases between taurolidine/heparin and control arms of LOCK-IT-100 Trial

	Taurolidine/ heparin (n=327)	Control (n=326)
No. of cases (CBRSI/1000 CD)	9 (0.13)	32 (0.46)
Total catheter-days follow-up	67,593	68,890
Hazard ratio (95% CI)*	0.29 (0.14, 0.62) p = 0.001	
Log-rank Test	p = 0.006	

*Cox Proportional Hazards Model
CD: Catheter Days; CI: Confidence Interval



- Taurolidine exhibited broad antimicrobial activity against all isolates tested, with 95.5% of all MIC values ≤1,024 µg/mL (Tables 2).
- All taurolidine MIC values were ≤ 1,024 µg/mL against Gram-positive bacteria:
  - *S. aureus* ($MIC_{50/90}$; 512/512µg/mL)
  - Coagulase-negative Staphylococcus ($MIC_{50/90}$; 512/512 µg/mL)
  - Enterococcus species ($MIC_{50/90}$; 512/512 µg/mL)
  - Viridans group streptococci ($MIC_{50/90}$; 512/512 µg/mL)
  - Non-tuberculosis Mycobacteria ($MIC_{50/90}$; 1,024/2,048 µg/mL)
  - Activity was maintained regardless of methicillin susceptibility for Staphylococcal isolates or vancomycin resistance among Enterococcal species.
- All taurolidine MIC values were ≤2,048 µg/mL against Gram-negative bacteria:
  - Enterobacterales ($MIC_{50/90}$; 512/512 µg/mL)
  - *P. aeruginosa* ($MIC_{50/90}$; 1,024/1,024 µg/mL)
  - *S. maltophilia* ($MIC_{50/90}$; 256/512 µg/mL)
  - *A. baumannii-calcoaceticus* sc ($MIC_{50/90}$; 512/512 µg/mL)
  - *Burkholderia cepacia* ($MIC_{50/90}$; 256/2,048 µg/mL)
  - Activity was maintained in multidrug-resistant Enterobacterales, *P. aeruginosa*, and *A. baumannii-calcoaceticus* sc isolates.
- All taurolidine MIC values were ≤1,024 µg/mL among *Candida glabrata* ($MIC_{50/90;}$ 512/512 µg/mL) and *Candida parapsilosis* ($MIC_{50/90;}$ 256/512 µg/mL) isolates
- $MIC_{50/90}$ values of 4,096/4,096 µg/mL were observed for *C. albicans*

Table 2. Distributions of taurolidine MIC values against various species/groups

	No. of isolates inhibited at a taurolidine MIC (µg/mL) of:								Taurolidine	
Organism (No. isolates)	**≤32**	**64**	**128**	**256**	**512**	**1,024**	**2,048**	**4,096**	**MIC_{50}**	**MIC_{90}**
S. aureus (76)				1	75				512	512
MSSA (37)					37				512	512
MRSA (39)				1	38				512	512
CoNS (52) [a]				10	38	4			512	512
S. epidermidis (36)					32	4			512	1,024
MSCoNS (21)				7	14				512	512
MRCoNS (31)				3	24	4			512	1,024
Enterococcus species (48)				6	40	2			512	512
E. faecalis (38)				1	35	2			512	512
E. faecium (10)				5	5				256	512
VRE (6) [b]				3	3				256	ND
Viridans group streptococci (18) [c]		1	2	5	10				512	512
Nontuberculous *Mycobacteria* (21)					7	7	7		1,024	2,048
M. avium complex (11) [d]						4	7		2,048	2,048
M. abcessus (10)					7	3			512	1,024
Enterobacterales (137)			1	22	106	8			512	512
E. coli (44)				1	43				512	512
K. pneumoniae (43)				2	38	3			512	512
P. mirabilis (10)				10					256	256
E. cloacae sc (10)					6	4			512	1,024
Citrobacter species (10)				9	1				256	256
S. marcescens (20)			1		18	1			512	512
MDR Enterobacterales (20) [e]	1			1	17	2			512	512
P. aeruginosa (45)					20	23	2		1,024	1,024
MDR *P. aeruginosa* (10)					8	2			512	1,024
S. maltophilia (15)				12	2	1			256	512
A. baumannii-calcoaceticus sc (15)				2	13				512	512
MDR *A. baumannii* sc (15)				1	5				512	ND
B. cepacia sc (15)				10	1	2	2		256	2,048
C. albicans (17)							5	12	4,096	4,096
C. glabrata (17)				3	13	1			512	512
C. parapsilosis (16)	3			9	4				256	512

[a] *Staphylococcus capitis* (2), *S. epidermidis* (36), *S. haemolyticus* (2), *S. lugdunensis* (10), and *S. saprophyticus* (2).
[b] *Enterococcus faecium* (6).
[c] *Streptococcus anginosus* group (2), *S. bovis* group (5), *S. gallolyticus* (2), *S. mitis* group (2), *S. salivarius* group (2), and *S. sanguinis* (5).
[d] *Mycobacterium avium* (5) and *Mycobacterium intracellulare* (5).
[e] *Enterobacter cloacae species complex* (2), *Escherichia coli* (9), and *Klebsiella pneumoniae* (9).

SUMMARY

- Taurolidine activity was very similar among a large collection of Gram-positive, Gram-negative, and yeast organisms.
- MIC90 values for all species/groups were ≤1,024 µg/mL, except for MAC and *B. cepacia* sc (MIC_{90}, 2,048 µg/mL) and *C. albicans* (MIC90, 4,096 µg/mL) where slightly higher MIC_{90} values were observed.
- The activity of taurolidine was unaffected by resistance to antibiotics (i.e., methicillin, vancomycin, or multi-drug resistance) among Gram-positive or Gram-negative organisms.
- Based on these data, catheter lock solutions containing the broad-spectrum antimicrobial taurolidine at 13,500 µg/mL have the potential to reduce the risk of CRBSI caused by a variety of species, including those observed in the recent LOCK-IT-100 clinical trial and other common bloodstream pathogens.