

Antistaphylococcal Activity of MK-2764 / PTK 0796 Compared to Other Agents

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ABSTRACT

Background: MK-2764 / PTK 0796 is a new antistaphylococcal agent with a broad spectrum of activity against gram-positive and gram-negative organisms. The activity of MK-2764 / PTK 0796, compared to those of vancomycin (VAN), linezolid (LIN), daptomycin (DAP), clindamycin (CLN), azithromycin (AZI), ceftriaxone (CEF) and levofloxacin (LEVO) against 112 strains of *S. aureus* was determined.

Methods:

The 112 strains comprised 24 MSSA and 88 MRSA (the latter including 3 VISA, 4 including the Hervey strain, and 5 VISA strains). MIC testing was as recommended by CLSI by agar diffusion on MH1 agar with added calcium for DAP testing. Inocula were 10⁸ c.f.u./loop and MICs read after overnight incubation at 35°C (a full 24 h for VAN).

Results: MIC₅₀ (µg/ml) were as follows:

Drug	Methicillin-susceptible (24)	Methicillin-resistant (88)
Range	MIC ₅₀	MIC ₅₀
MK-2764/PTK 0796	0.25-2	0.06-2
Vancomycin	0.5-2	1
Linezolid	1-2	1
Daptomycin	0.12-1	0.5
Clindamycin	0.12-32	>32
Azithromycin	1-64	>64
Ceftriaxone	1-128	>128
Levofloxacin	0.12-32	2

All strains, regardless of phenotype, were susceptible to MK-2764 / PTK 0796, with MICs ranging from 0.06-2 µg/ml. LIN and DAP were also potent against all strains, with MIC ranges between 0.5 - 4 µg/ml and 0.12-4 µg/ml, respectively. VAN MIC ranges against all strains, with MIC ranges between 0.5-2 µg/ml and all strains, except clonal MRSA organisms, showed resistance to clindamycin, CLN, AZI and LEVO.

Conclusions:

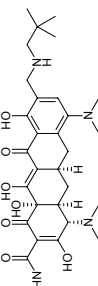
MK-2764 / PTK 0796, a new antistaphylococcal agent, was potent against all *S. aureus* strains tested, irrespective of phenotype.

INTRODUCTION

Staphylococcal production in staphylococcal strains, especially those acquired in the hospital, is the rule. All staphylococcal strains are susceptible to vancomycin, daptomycin, linezolid, and MK-2764 / PTK 0796. All staphylococcal strains are increasingly resistant to hospital practice. These strains are not only resistant to all antibiotics but are also always resistant to quinolones such as ciprofloxacin, levofloxacin, moxifloxacin and gatifloxacin.

The first few years have witnessed an extremely worrisome increase of rifampicin-resistant infections caused by common, non-sequenced methicillin-resistant *S. aureus* strains producing Panton-Vilchins toxin. Although these strains are currently more susceptible than are hospital-acquired strains, this situation will doubtless change. Although glycopeptide therapy is effective for the latter strains, there has been the appearance of strains that are both trimethoprim and daptomycin drug resistant to glycopeptides, such as vancomycin and teicoplanin. The true nature of these strains (epidemiology) is still unclear. It is very likely that the already reported drug resistance in staphylococcal strains and laboratory detection of these strains.

MK-2764 / PTK 0796 is a new antistaphylococcal agent with a broad spectrum of activity against Gram-positive and Gram-negative organisms (1). MIC testing was as recommended by CLSI by agar diffusion on MH1 agar with added calcium for DAP testing. Inocula were 10⁸ c.f.u./loop and MICs read after overnight incubation at 35°C (a full 24 h for VAN). In this center study, the susceptibility of 112 clonal methicillin susceptible and 88 resistant *S. aureus* (the latter including multiple drug VISA and five VISA) to MK-2764, azithromycin, levofloxacin, vancomycin, linezolid, daptomycin, clindamycin, ceftriaxone and amoxicillin-clavulanic acid were tested by agar diffusion MIC.



METHODS

Organisms to be tested and drugs: Susceptibility powders were obtained from their respective manufacturers. Of a total of 112 strains, 24 were methicillin susceptible and 88 (including three VISA and five VISA strains) were methicillin resistant.

Susceptibility testing: Agar diffusion methodology according to CLSI (M7-A9) (Heron Agar Suspension) with turbidity equivalent to a 0.5 McFarland standard were scraped from blood agar plates, suspended and diluted to obtain a final inoculum of 1 x 10⁸ c.f.u./loop.

Calcium was added for daptomycin testing to a final concentration of 50 µg/ml. Plates were incubated overnight in air at 35°C with full 24 h incubation for vancomycin. Strains of group 2 (MRSA) were included in each run.

RESULTS

Cumulative MICs can be seen in Table 1. As shown, MK-2764 MICs all ranged between 0.06 and 2 µg/ml irrespective of the strain's genotype or phenotype.

Resistance to azithromycin, clindamycin, amoxicillin / clavulanic acid, levofloxacin and ceftriaxone was commonly seen.

MK-2764 was consistently exhibited potent activity against *S. aureus* isolates regardless of susceptibility by to other agents.

Table 1: Cumulative MICs (µg/ml) of drugs tested

Drug	Methicillin susceptible (24)		Methicillin resistant (88)	
	Range	MIC ₅₀	Range	MIC ₅₀
MK-2764	0.25-2	0.5	0.06-2	0.5
Azithromycin	1-64	16	0.5-64	>64
Clindamycin	0.12-32	0.25	<=0.06-32	>32
Amoxicillin-clavulanic acid	0.25-16	0.5	0.5-16	>16
Levofloxacin	0.12-32	2	1-32	>32
Linezolid	1-2	2	0.5-4	2
Vancomycin	0.5-2	1	0.5-256	1
Ceftriaxone	1-128	4	>128	>128
Daptomycin	0.12-1	0.5	0.12-4	0.5

Figure 1. Cumulative % Inhibition of *S. aureus* (n=112)

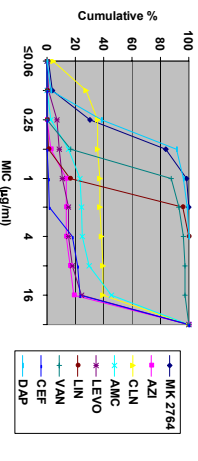


Table 2: Activity of MK-2764 vs. VISA and MRSA Isolates

INMIC#	MK-2764	VAN	LIN	DAP	AZI	CLN	LEVO	CEF	Mech
SAS504	0.5	8.0	2.0	2.0	16	0.12	32	64	R
SAS505	1.0	4.0	2.0	4.0	>64	>32	16	>128	R
SAS506	1.0	4.0	1.0	2.0	>64	0.25	16	>128	R
SAS507	1.0	4.0	2.0	2.0	>64	>32	32	>128	R
SAS508	0.5	4.0	2.0	1.0	>64	>32	32	>128	R
SAS509	1.0	256	2.0	0.5	>64	>32	16	>128	R
SAS510	0.5	128	2.0	1.0	16	8.0	2.0	>128	R
SAS512	1.0	128	2.0	0.5	8.0	4.0	2.0	8.0	R

The activity of MK-2764 against *S. aureus* was not affected by vancomycin resistance. MK-2764 was the most active compound against the isolates tested.

Figure 2. Cumulative % Inhibition of MRSA (n=88 Isolates)

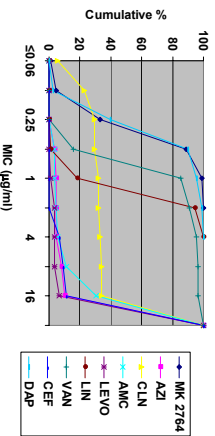
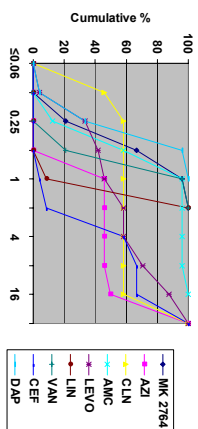
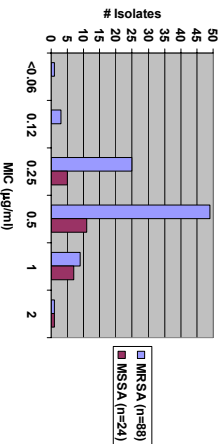


Figure 3. Cumulative % Inhibition of MSSA (N=24 Isolates)



Significant ranking of the population MICs under the presence of VISA and MRSA in the study set. MK-2764 did not show a corresponding effect, indicative of potent activity and lack of impact of resistance to other agents.

Figure 4. Susceptibility of *S. aureus* to MK 2764



The MIC distribution of MK-2764 was similar for MSSA and MRSA. The modes of each distribution were 0.5 µg/ml.

CONCLUSIONS

MK-2764 was active against all staphylococcal tested regardless of their susceptibility to other agents at MICs < 2 µg/ml.

If results of pharmacokinetic/pharmacodynamic and animal toxicity and therapeutic studies look positive, MK-2764 / PTK 0796 seems to be a promising agent for treatment of infections caused by drug-resistant *S. aureus* in strains of all phenotypes.

MK-2764 is currently undergoing evaluation as an oral agent. Of the orally available antistaphylococcal tested, only MK-2764 exhibited reasonable activity against these isolates, although less potent than MK-2764.