

Prevalence of Inducible Clindamycin Resistance in Staphylococcal Isolates at a Korean Tertiary Care Hospital

Hwan Sub Lim,¹ Hyukmin Lee,¹ Kyoung Ho Roh,² Jong Hwa Yum,² Dongeun Yong,² Kyungwon Lee,² and Yunsop Chong²

¹Department of Laboratory Medicine, Kwandong University College of Medicine, Kyunggi, Korea;

²Departments of Laboratory Medicine and Research Institute of Bacterial Resistance, Yonsei University College of Medicine, Seoul, Korea.

Clindamycin resistance in *Staphylococcus* species can be either constitutive or inducible. Inducible resistance cannot be detected by the conventional antimicrobial susceptibility test. In this study, we determined the prevalence of inducible clindamycin resistance in staphylococcal isolates at a Korean tertiary care hospital. Between February and September 2004, 1,519 isolates of *Staphylococcus aureus* and 1,043 isolates of coagulase-negative staphylococci (CNS) were tested for inducible resistance by the D-zone test. Overall, 17% of MRSA, 84% of MSSA, 37% of MRCNS, and 70% of MSCNS were susceptible to clindamycin. Of the erythromycin non-susceptible, clindamycin-susceptible isolates, 32% of MRSA, 35% of MSSA, 90% of MRCNS, and 94% of MSCNS had inducible clindamycin resistance. Inducible clindamycin resistance in staphylococci was highly prevalent in Korea. This study indicates importance of the D-zone test in detecting inducible clindamycin resistance in staphylococci to aid in the optimal treatment of patients.

Key Words: *Staphylococcus*, clindamycin, antibiotic resistance

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a notorious nosocomial pathogen prevalent in many countries. A study by the Korean Nationwide Surveillance of Antimicrobial Resistance (KONSAR) program showed that 68% of *S. aureus* isolates in 2003 were methicillin-resistant.¹ Vanco-

mycin has been used increasingly to treat MRSA infections. Dissemination of vancomycin-resistant enterococci was considered to be partly due to increased vancomycin use. Rapid increase in vancomycin resistance necessitates the restriction of vancomycin usage, as well as encourages treatment with older antimicrobial agents, such as trimethoprim-sulfamethoxazole and clindamycin. Clindamycin, a lincosamide antibiotic active against gram-positive microorganisms including staphylococci and streptococci, inhibits bacterial protein synthesis. It can be administered orally to treat mild infections in children or soft tissue infections.²⁻⁴ The clindamycin resistance mechanism is primarily due to ribosomal modification by methylases encoded by *erm* genes. Methylation of 23S rRNA decreases the affinity for clindamycin, all macrolides, and type B streptogramins (the MLS_B phenotype).⁵ Some of the enzymes are constitutively regulated, while others are inducibly regulated by translational attenuation of a mRNA leader sequence. In the absence of erythromycin, the mRNA is in an inactive conformation due to a sequestered Shine-Dalgarno sequence, preventing the efficient initiation of translation of *erm* transcripts.⁶

Constitutive resistance can be readily detected, but inducible resistance is not detectable by routine antimicrobial susceptibility tests.^{7,8} The Clinical and Laboratory Standards Institute (CLSI) recommends testing for inducible clindamycin resistance in isolates of staphylococci by using a D-zone test.⁹ This test is important for optimal treatment of patients, but the prevalence of in-

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Reprint address: requests to Dr. Kyungwon Lee, Department of Laboratory Medicine, Yonsei University College of Medicine, 134 Shinchon-dong, Seodaemun-gu, Seoul 120-752, Korea. Tel: 82-2-2228-2446, Fax: 82-2-313-0908, E-mail: leekcp@yumc.yonsei.ac.kr

ducible clindamycin resistance has not yet been reported in Korea. Aim of this study was to determine the prevalence of inducible clindamycin resistance in *S. aureus* and coagulase-negative staphylococci (CNS) isolated from patients in a tertiary care hospital in Korea.

MATERIALS AND METHODS

Between February and September 2004, non-duplicate *S. aureus* and CNS were isolated from patients in a tertiary care university hospital in Korea. The species were identified by conventional methods using a coagulase tube, mannitol-salt agar, and DNase agar or by using the Vitek GPI card system (bioMerieux, Marcy l'Etoile, France). Antimicrobial susceptibilities were determined by the CLSI disk diffusion method.⁹ To detect inducible clindamycin resistance, the D-zone test was performed. A staphylococcal suspension equivalent to 0.5 McFarland turbidity was used to inoculate a Mueller-Hinton agar (MHA) plate. Then, 2- μ g clindamycin and 15- μ g erythromycin disks (Becton- Dickinson Microbiology Systems, Cockeysville, MA, USA) were placed 15 mm apart (margin to margin).¹⁰ After an 18-hour incubation at 35°C, a D shaped blunting of the clindamycin disk inhibition zone adjacent to the erythromycin disk was interpreted as positive.

RESULTS

Overall, the antimicrobial resistance rates of *S. aureus* and CNS in 2004 at the tertiary care hospital were 59% and 54% to oxacillin (data not shown). The resistance rates of MRSA and methicillin-susceptible *Staphylococcus aureus* (MSSA) were as follows: 77% and 4% to clindamycin, 90% and 26% to erythromycin, 22% and 1% to cotrimoxazole, 66% and 14% to tetracycline, and 84% and 10% to fluoroquinolone, respectively. Resistance rates of CNS are shown in Table 1.

The percentages of strains with constitutive and inducible clindamycin resistance were as follows: 79% and 4% of MRSA, 6% and 9% of MSSA, 33% and 30% of MRCNS, and 9% and 21% of methicillin-susceptible coagulase-negative staphylococci

(MSCNS), respectively (Table 2). Of the erythromycin non-susceptible but clindamycin-susceptible isolates, 32% of MRSA, 35% of MSSA, 90% of MRCNS, and 94% of MSCNS were inducibly clindamycin resistant.

DISCUSSION

In the present study, the resistance rates of methicillin-susceptible staphylococci to clindamycin, erythromycin, tetracycline, and fluoroquinolone were much lower than those of methicillin-resistant isolates. However, in general, tetracyclines and fluoroquinolones are not recommended for the treatment of pediatric patients and pregnant women because of possible side effects. It is noteworthy that clindamycin susceptible rates were higher than those of erythromycin, regardless of methicillin susceptibility.

Clindamycin is indicated for the treatment of soft tissue infections, pediatric infections caused by staphylococci, or for patients allergic to β -lactam agents.²⁻⁴ Inducible clindamycin-resistant staphylococci show susceptible results in conventional susceptibility tests, but can be converted to a constitutively resistant phenotype during clindamycin treatment.^{11,12} As the resistance conversion may result in clindamycin treatment failure,^{13,14} detection of inducible clindamycin resistance is necessary.⁹ Inducible clindamycin resistance can be detected only by the D-zone test.^{7,8} When a D-zone test shows a distorted zone of inhibition around a clindamycin disk by erythromycin, the isolate is considered to be inducible clindamycin resistance.

Possible variations in the prevalence of constitutive and inducible clindamycin resistance have been reported depending on regional and bacterial species.^{11,14,15} In our study, the rate of inducible clindamycin resistance in erythromycin non-susceptible and clindamycin-susceptible staphylococcal isolates was 63% (data not shown); this was similar to 62% in Iowa¹¹ and 56% in Maryland¹⁴ in the USA. Schreckenberger reported that inducible clindamycin resistance was more prevalent in MRSA.¹⁵ However, in our study; inducibly clindamycin-resistant strains were more prevalent in CNS (91%) than in MRSA (32%). Our

Table 1. Antimicrobial Susceptibility of Staphylococci Isolated between February and September 2004

Organism (No. tested)/Antimicrobial agents	Susceptibility (%)		
	Susceptible	Intermediate	Resistant
Methicillin-resistant <i>S. aureus</i> (888)			
Clindamycin	21	2	77
Erythromycin	8	2	90
Trimethoprim-sulfamethoxazole	77	1	22
Tetracycline	33	1	66
Fluoroquinolone	8	8	84
Methicillin-susceptible <i>S. aureus</i> (631)			
Clindamycin	94	2	4
Erythromycin	68	6	26
Trimethoprim-sulfamethoxazole	98	1	1
Tetracycline	85	1	14
Fluoroquinolone	69	21	10
Methicillin-resistant coagulase-negative staphylococci (560)			
Clindamycin	67	6	27
Erythromycin	34	1	65
Trimethoprim-sulfamethoxazole	51	2	47
Tetracycline	66	2	32
Fluoroquinolone	39	8	53
Methicillin-susceptible coagulase-negative staphylococci (483)			
Clindamycin	92	5	3
Erythromycin	69	4	27
Trimethoprim-sulfamethoxazole	89	1	10
Tetracycline	67	4	29
Fluoroquinolone	79	1	20

data indicate that if the D-zone test is not performed, 32% of MRSA, 35% of MSSA, 90% of MRCNS, and 94% of MSCNS isolates with an erythromycin non-susceptible and clindamycin-susceptible pattern are mistakenly interpreted as clindamycin susceptible, possibly resulting in treatment failure.

Almer reported that inducible clindamycin resistance in CA-MRSA was relatively prevalent (28%).¹⁶ In this study, there were no significant differences between inpatient and outpatient

incidences of inducible clindamycin resistance of staphylococci, except for MRSA. The higher prevalence of inducible clindamycin resistance in outpatient isolated MRSA is not clear, but it is possible that the isolates are, in reality, hospital-associated strains.

In summary, 32-35% of erythromycin non-susceptible and clindamycin-susceptible *S. aureus* and 90-94% of erythromycin non-susceptible and clindamycin-susceptible CNS showed inducible resistance to clindamycin. This study indicates the

Table 2. Prevalence of Constitutive and Inducible Clindamycin Resistance in Staphylococcal Isolates

Organism	Patient	No. of isolates tested	No. (%) of isolates			
			EM-S, CLN-S	EM-R, CLN-R	EM NS, CLN-S*	
					IND Pos	IND Neg
MRSA	Inpatient	558	47 (8)	436 (78)	14 (19)	61 (81)
	Outpatient	330	27 (8)	265 (80)	22 (58)	16 (42)
	Total	888	74 (8)	701 (79)	36 (32)	77 (68)
MSSA	Inpatient	297	198 (67)	26 (9)	25 (34)	48 (66)
	Outpatient	334	228 (68)	14 (4)	33 (36)	59 (64)
	Total	631	426 (68)	40 (6)	58 (35)	107 (65)
MRCNS	Inpatient	302	94 (31)	104 (34)	98 (94)	6 (6)
	Outpatient	258	94 (36)	82 (32)	69 (84)	13 (16)
	Total	560	188 (34)	186 (33)	167 (90)	19 (10)
MSCNS	Inpatient	269	206 (77)	12 (5)	47 (92)	4 (8)
	Outpatient	214	128 (60)	29 (14)	54 (95)	3 (5)
	Total	483	334 (69)	41 (9)	101 (94)	7 (6)

*Percentages indicated are among erythromycin-nonsusceptible and clindamycin-susceptible isolates.

MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; MRCNS, methicillin-resistant coagulase-negative staphylococci; MSCNS, methicillin-susceptible coagulase-negative staphylococci; EM, erythromycin; CLN, clindamycin; S, susceptible; R, resistant; NS, nonsusceptible; IND, induction; Pos, positive; Neg, negative.

importance of the D-zone test to differentiate inducibly clindamycin-resistant isolates of staphylococci to facilitate the optimal treatment of patients.

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