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Resistance status of antibiotics in Gram-positive bacteria isolated from acne lesions in İstanbul

İstanbul'da akne lezyonlarından izole edilen Gram-pozitif bakterilerin antibiyotiklere direnç durumu

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Abstract

Background and Design: Acne vulgaris is a multifactorial disease in which *Propionibacterium acnes* is thought to play an important role in the pathogenesis of inflamed lesions. There is also significant *in vitro* evidence suggesting a possible pathogenetic role for Staphylococci in acne vulgaris and an *in vitro* study of patients who were undergoing evaluation for acne, showed that 53% of participants were colonised with *Staphylococcus epidermidis*.

Materials and Methods: In this study, 29 *P. acnes* isolates and 61 coagulase-negative staphylococci (CNS) isolates were obtained from 169 specimens belonging to patients with inflammatory acne vulgaris and the antimicrobial susceptibilities of these isolates against nadifloxacin, erythromycin, clindamycin and tetracycline were determined at the minimum inhibitory concentration levels, using the 'Clinical and Laboratory Standards Institute' agar dilution method.

Results: There were no *P. acnes* isolate resistant to the antibiotics tested in this study and the antibiotic resistance status among CNS was as 28%, 36%, 23% and 0% for tetracycline, erythromycin, clindamycine and nadifloxacin, respectively.

Conclusion: According to the results of this study, it may be expected that nadifloxacin could be more effective in the treatment of acne than other antimicrobial agents because of having no resistance to both *P. acnes* and CNS. However, this must be supported by clinical trials. Although resistance rates were found to be relatively low in this study, the antibiotic resistance problem should be taken into consideration while planning a treatment to get successful results. In case of treatment failures, presence of drug resistant strains should be considered.

Keywords: Antibiotic resistance, topical, acne, İstanbul

Öz

Amaç: Akne vulgaris, inflame lezyonların patogenezinde *Propionibacterium acnes*'in önemli bir rol oynadığı düşünülen multifaktöriyel bir hastalıktır. Ayrıca stafilokokların da akne vulgariste olası patogenetik rolü olduğuna dair önemli *in vitro* bulgular vardır. Yapılan bir çalışmada, akne açısından değerlendirilen katılımcıların %53'ünün *Staphylococcus epidermidis* ile kolonize olduğu gösterilmiştir.

Gereç ve Yöntem: Bu çalışmada enflamatuvar akneli hastalardan sağlanan 169 örnekten, 29 *P. acnes* ve 61 koagülaz negatif stafilokok (KNS) izolatı elde edilmiş ve bu izolatların nadifloksasin, eritromisin, klindamisin ve tetrasikline karşı antimikrobiyal duyarlılıkları Klinik ve Laboratuvar Standartları Kurumu 'Clinical and Laboratory Standards Institute' agar dilüsyon metodu kullanılarak minimum inhibisyon konsantrasyonu seviyesinde belirlenmiştir.

Bulgular: Hiçbir *P. acnes* izolatı bu çalışmada kullanılan antibiyotiklere dirençli değildi. KNS izolatlardaki direnç durumu ise tetrasiklin, eritromisin, klindamisin ve nadifloksasine karşı sırasıyla %28, %36, %23 ve %0 olarak saptandı.

Sonuç: Bu çalışma verilerine göre, nadifloksasine karşı *P. acnes* ve KNS izolatlarında herhangi bir direnç saptanmaması nedeniyle, nadifloksasinin akne tedavisinde daha etkili olabileceği düşünülebilir. Fakat böyle bir sonucun klinik çalışmalarla desteklenmesi gerekir. Bizim çalışmamızdaki direnç oranları düşük çıkmış olsa bile, akne tedavisi planlanırken başarılı sonuçlar alabilmek için direnç problemi de göz önünde bulundurulmalıdır. Tedavi başarısızlıklarında ilaca dirençli suşların varlığı akla gelmelidir.

Anahtar Kelimeler: Antibiyotik direnci, topikal, akne, İstanbul

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Introduction

Acne vulgaris is one of the most common skin diseases, predominantly seen in adolescence and also a multifactorial disease in which *Propionibacterium acnes* is thought to play an important role in the pathogenesis of inflamed lesions[1]. There is also significant *in vitro* evidence suggesting a possible pathogenetic role for *Staphylococci* in acne vulgaris and in an *in vitro* study investigating samples from the normal skin and pustular and nodulocystic skin lesions obtained from 100 college students, *Staphylococcus epidermidis* was detected in 53% of samples[2].

Antibiotics have been used for over 40 years and are still widely prescribed for acne treatment. Studies from different countries such as the Netherlands, Sweden, United Kingdom, United States, New Zealand and Japan have suggested a clear association between the emergence of resistance to clindamycin, tetracyclines, erythromycin and trimethoprim-sulfamethoxazole in *P. acnes* and the therapeutic use of these antibiotics[3-5]. A recent European study showed that prescribing practices for acne affect resistant rates especially to tetracyclines, and also topical formulations of erythromycine and clindamycine used for acne treatment induce a significant dissemination of cross-resistant *P. acnes* strains. The highest resistant rates were found in Spain (94%), and lowest in Hungary (51%)[6]. In another study carried out in Stockholm, the prevalence of resistant *P. acnes* strains in antibiotic-treated patients was notably higher than in non-antibiotic-treated acne patients (37% and 13%, respectively)[3]. Nadifloxacin is another relatively new topical antibiotic, a third-generation fluorinated quinolone, widely used for the treatment of inflamed acne lesions and it has a potent bactericidal activity against *P. acnes* and other Gram-positive and Gram-negative bacteria. The data on the resistance to nadifloxacin is rare[7,8].

A large number of studies have shown that many acne patients are colonized by resistant bacterial strains and this issue is crucial for a correct selection of treatment[9-12].

The aim of this study was to evaluate the bacterial resistance status of different antibiotic drugs, especially nadifloxacin for which the data is sparse, used topically for acne in İstanbul region which is a sample of Turkish population, by means of quantitative microbiology techniques.

Materials and Methods

The study were approved by the Sultan Abdülhamid Han Training and Research Hospital of Ethics Committee (protocol number and date 23.02.2012/13).

In this study, 29 *P. acnes* isolates and 61 coagulase-negative staphylococci (CNS) isolates were obtained from 169 specimens belonging to the patients with inflammatory acne vulgaris recruited from department of dermatology within a period of 8 months and the antimicrobial susceptibilities of these isolates against a number of antibiotics, including nadifloxacin, erythromycin, clindamycin and tetracycline, were determined at the minimum inhibitory concentration (MIC) level, using the Clinical and Laboratory Standards Institute (CLSI) agar dilution method. The specimens were obtained from the acne lesions on the patients' skin, using an insulin syringe under aseptic conditions and transferred to the microbiology laboratory in 'Amies' transport medium. Twin specimens were obtained from each patient and one of the specimens was inoculated into *Brucella* blood agar (BD, USA) as well as into regenerated thioglycolate broth (Oxoid, United Kingdom) and incubated in an anaerobic chamber (Bactron, Shellab 4, USA) for 48-72 hours at 37 °C, in order to isolate *P. acnes*. The second specimen was inoculated into 5% sheep blood agar (Salubris, Turkey) and incubated aerobically for 18 to 24 hours at 37 °C to isolate aerobic agent. The identification of *Staphylococcus* species was performed by using conventional methods such as Gram staining, catalase, coagulase and DNase tests. Gram stains and subcultures of the anaerobically growing colonies were also performed to identify *P. acnes*. One of the subculture plates was left in the anaerobic medium while another one was stored in aerobic conditions to assess the aerotolerance of the bacteria. Gram positive and catalase positive colonies of bacteria in shape of diphtheroid bacillus which fail to grow aerobically were predefined as *P. acnes*. Definite identification was performed by using Vitek 2 ANC (Biomerieux, France) anaerobe identification cards. Identified isolates were stored in 20% skim milk (BD, USA) at -80 °C until tested for susceptibility.

Antibiotics in powder form with known potency, including tetracycline (Sigma-Aldrich, China), erythromycin (Sigma-Aldrich, China), clindamycin (Sigma-Aldrich, China), and nadifloxacin (Otsuka Pharmaceutical Co, Japan) were used for susceptibility testing. Stock solutions for the antibiotics were prepared with appropriate solvents and diluents according to the manufacturer's instructions. Stock solutions were stored at -80 °C until tested. *Brucella* agar containing 5% lysed human blood (provided from the blood center at our hospital), 5 mg/L hemin (Serva, Germany) and 1 mg/L vitamin K (Sigma, China) were used for *P. acnes*, as an appropriate medium for agar dilution technique, while Mueller Hinton agar (BD, USA) was used for *Staphylococci*. Nadifloxacin, erythromycin, clindamycin and tetracycline stock solutions prepared for *P. acnes* were used in media containing 0.032 to 8 µg/mL of each antibiotic in order to determine their efficacy against *P. acnes*. While the concentrations of erythromycin, clindamycin and tetracycline were ranging from 0.128 to 64 µg/mL in the media for *Staphylococci* isolates, it was ranging from 0.032 to 8 µg/mL in the media containing nadifloxacin. The inoculation number for the test was 10^5 CFU per field for *P. acnes*. The concentration of bacterial suspensions of *Staphylococci* ($1.5x10^8$ CFU) was also equivalent to 0.5 McFarland standard in the suspension turbidity detector (Den-1, Biosan-Lithuania). Following inoculation, *P. acnes* inoculated plates were immediately transferred to an anaerobic chamber and incubated for 48 to 72 hours at 37 C and *Staphylococci* plates were incubated aerobically for 18 to 20 hours at 35±2 °C. MIC 50 and MIC 90 values for each antibiotic were calculated following incubation separately. In addition, methicillin resistance among *Staphylococci* species was tested by cefoxitin 30 µg disc (Bioanaliz, Turkey) and inducible clindamycin resistance was tested by clindamycin 2 µg and erythromycin 15 µg discs (Bioanaliz, Turkey), using the disc diffusion method in Mueller-Hinton agar according to the CLSI recommendations to determine the presence of "D zone". The control species were American Type Culture Collection (ATCC) 11827, ATCC 29213, and ATCC 12228 for *P. acnes, S. aureus* and *S. epidermidis*, respectively.

Based on the MIC values determined according to the CLSI and European Committee on Antimicrobial Susceptibility Testing criteria for agar dilution, the reference ranges for the antimicrobial susceptibility of the test bacteria were as in Table 1.

Results

In this study, the specimens were obtained from a total of 169 patients and 101 causative agents were isolated in 89 patients (53%). The causative agents were *P. acnes* in 28 patients (31%), CNS in 49 patients (56%) and both pathogens in 12 patients (13%): *P. acnes* was associated with methicillin resistant CNS in 8 cases and methicillin-sensitive CNS in 4 cases (Table 2). 11 out of 40 (28%), *P. acnes* isolates were found to be non-vital while revitalizing from the stock solutions. Therefore, the susceptibility testing and analyses were performed in the remaining 29 *P. acnes* isolates. The MIC values of the antibiotics for CNS and *P. acnes* isolates are shown in Table 3. The results showed that nadifloxacin was very effective against the CNS isolates, because the inhibition concentration of 25 isolates were <0.032 µg/mL and that of the rest was <4 µg/mL. The values for the other antibiotics were between <0.128 and <32 µg/mL (Table 4). The results also showed that the inhibition concentrations of 17 and 12 *P. acnes* isolates were <0.032 µg/mL for nadifloxacin and erythromycine. Although the greatest MIC values of *P. acnes* for these two antibiotics were <0.128 µg/mL, there were 19 and 8 *P. acnes* isolates of which MIC values were >0.128 µg/mL for tetracycline and clindamycin (Table 4).

There was no *P. acnes* isolate resistant to the antibiotics tested in this study and the antibiotic resistance status in CNS is shown in Table 5. Inducible clindamycin resistance was additionally shown in 7 (11%); 6 CNS isolates were methicillin-resistant and 1 was methicillin-sensitive. These isolates were considered also resistant and included in that group.

Discussion

Most patients with mild to moderate acne are generally being treated with topical drugs as first-line treatment. Topical antibacterials are used mainly to reduce the population of *P. acnes* on the skin surface and in particular within the follicles[13-15]. The number of studies about developing of resistance to nadifloxacin is not as many as the number of those on the other aforementioned antibiotics. In one of them, conducted in 1995, Bojar et al.[16] showed that the proportion of resistant *Propionibacteria* isolated from the erythomycin-treated group increased significantly and this fact drew attention to the antibiotic resistance problems at that time. In another similar study by Plewig et al.[17], it has been reported that there was extremely low number of nadifloxacin-resistant microorganisms compared to erythromycine.

In some studies performed between 2000 and 2005 in different countries of Europe, the reported rates of resistant *P. acnes* against different antibiotics ranged from 13 to 94%[3,6,18]. Ross et al.[6] have also showed that combined resistance to clindamycin and erythromycin was much more common (highest prevalence 91% in Spain) than resistance to the tetracyclines (highest prevalence 26.4% in the U.K.). The European surveillance study on the antibiotic susceptibility of *P. acnes* was conducted by Oprica and Nord[18] in 13 European countries. Of the isolates examined, 2.6% were resistant to tetracycline, 15.1% to clindamycin, and 17.1% to erythromycin. Nevertheless, the rates of resistant strains among the countries varied considerably, ranging from 83% in Croatia to 0% in the Netherlands[18].

In studies performed between 2011 and 2013, the prevalence of resistant *P. acnes* against antibiotics ranged from 0 to 53.5%[19-22]. Two studies performed one year apart in Korea showed very different rates of resistance to one or other of the antibiotics tested against *P. acnes* (0% and 36.7%). A higher proportion of *P. acnes* isolates were significantly resistant to clindamycin (30%) and erythromycin (26.7%) compared with other antibiotics tested[19,20]. Schafer et al.[22] have

Table 1. Reference ranges of the antimicrobial susceptibility of the test bacteria (Clinical and Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing)

	Erythromycin		Clindamycin		Tetracycline		Nadifloxacin	
	Susceptible	Resistant	Susceptible	Resistant	Susceptible	Resistant	Susceptible	Resistant
P. acnes	≤0.5 µg/mL	≥8 µg/mL	≤2 µg/mL	≥8 µg/mL	≤4 µg/mL	≥16 µg/mL	≤1 µg/mL	≥4 µg/mL
CNS*	≤0.5 µg/mL	≥8 µg/mL	≤0.5 µg/mL	≥4 µg/mL	≤4 µg/mL	≥16 µg/mL	≤1 µg/mL	≥4 µg/mL

*CNS: Coagulase-negative staphylococci, *P. acnes: Propionibacterium acnes*

Table 2. Disribution of causative agents

Causative agent	n (Case)
P. acnes	28
CNS	49
P. acnes + CNS	12 (12 *P. acnes* + 12 CNS)
Total causative agents	101 (40 P. acnes + 61 CNS)

CNS: Coagulase-negative staphylococci, *P. acnes: Propionibacterium acnes*

Table 3. MIC 50 ve MIC 90 values (µg/mL)* for *P. acnes* and coagulase-negative staphylococci

		Tetracycline	Erythromycin	Clindamycin	Nadifloxacin
P. acnes	MIC 50	0.25	0.064	0.125	<0.032
	MIC 90	0.5	0.125	0.5	0.064
CNS	MIC 50	0.5	1	0.5	0.064
	MIC 90	32	8	4	0.5

P. acnes: Propionibacterium acnes, MIC: Minimum inhibitory concentration, *MIC 50 and MIC 90 represent the MIC value at which ≥50% and ≥90% of the isolates in a test population are inhibited respectively

demonstrated that all clindamycin-resistant strains had cross-resistance to erythromycin and the use of topical erythromycin or clindamycin was a risk factor for carrying resistant strains. Moreover, in another study by Nakase et al.[23], it was shown that more than 80% of patients who carried clindamycin-resistant *P. acnes* also carried clindamycin-resistant *S. epidermidis*.

In other studies including nadifloxacin performed in extended intervals, no *P. acnes* strain resistant to nadifloxacin was reported. Gübelin et al.[24] studied the antimicrobial susceptibility of 53 strains of *P. acnes* isolated from inflammatory acne. All isolates were susceptible to penicillin, minocycline and nadifloxacin, but there was erythromycin and clindamycin resistance in 3.8% and 1.9% of isolates, respectively. Alba et al.[25] conducted a study to analyse the evolution of resistance of nadifloxacin against several Gram-positive bacteria in Germany. The results showed that the resistance rate to nadifloxacin had not increased and no resistant strains appeared during 3 years use of this antibiotic in Germany, while 28% and a 10% of strains were resistant to erythromycin and clindamycin, respectively. On the other hand, while the rate of resistance of *S. epidermidis* to nadifloxacin was found to be 0% between 2000 and 2008, it was reported to be 10.3% between 2008 and 2010 in a study performed in Japan. Erythromycin and clindamycin presented much higher rates of resistance (58.6 and 51.7%, respectively) in the latter study[23].

There was no *P. acnes* isolate resistant to the antibiotics tested in our study, and the resistance rates of CNS to erythromycin, tetracycline, clindamycin, and nadifloxacin were 36, 28, 23 and 0%, respectively. Moreover, lower nadifloxacin concentrations could be tested for CNS because of having 25 isolates in which MIC values were <0.032 µg/mL. It could be said in other words that CNS was very sensitive to nadifloxacin. Lower concentrations for *P. acnes* could also be tested for erythromycin and nadifloxacin because of having 12 and 17 isolates in which MIC values were <0.032 µg/mL (Table 4). This also can be understood as that *P. acnes* was more sensitive to nadifloxacin and erythromycin than the other two antimicrobial agents, tetracycline and clindamycine. According to the results obtained in this study, to date, there has been no evidence of resistance to nadifloxacin against *P. acnes* and CNS strains in Istanbul. Consequently, nadifloxacin can be safely used in acne and CNS infections by considering the resistance problem. One of the major drawbacks to using topical antibacterials has been the dramatic increase in bacterial drug resistance over the past decades. The concern that topical application of nadifloxacin would lead to the development of drug resistance of the whole group of quinolones and limit their applicability in systemic treatments is still not justified although this argument could also be applied to other antibiotics. Furthermore, this gyrase inhibitor can be combined with topical retinoids or benzoyl peroxide to limit antibiotic resistance in the treatment of mild to moderate acne vulgaris as is the case with the other topical antibiotics[26-28]. It is also suggested that fast therapeutic results may reduce the risk of developing bacterial resistance[28]. Additionally, the administration of topical and oral antibiotics should be limited to the shortest possible period.

It has been shown that the level of antimicrobial resistance can differ from one city to another and even between hospitals in the same city[19]. Therefore, these kind of studies should be performed by at least on the country bases at specific intervals and the rates should be evaluated on the local basis. In accordance with that fact, this study pretends to be one of the leading studies performed in Turkey which is a country settled partly in Europe, with the objective to stimulate discussion concerning the resistance matter and to speed up developing strategies to struggle for rising problem of antibiotic resistance in *P. acnes* and other microorganisms.

Ethics

Ethics Committee Approval: The study were approved by the Sultan Abdülhamid Han Training and Research Hospital of Ethics Committee (protocol number and date 23.02.2012/13).

Table 4. The numbers of inhibited coagulase-negative staphylococci and *P. acnes* isolates in every tested minimum inhibitory concentration value (µg/mL)

MIC	<0.032		0.064		0.128		0.25		0.5		1		2		4		8		16		32	
	CNS	PA	CNS	PA	CNS	PA	CNS	PA	CNS	PA	CNS	PA	CNS	PA	CNS	PA	CNS	PA	CNS	PA	CNS	PA
Tetracycline	-	2	-	3	8	5	12	9	14	10	8	-	3	-	1	-	1	-	5	-	9	-
Erythromycin	-	12	-	14	11	3	4	-	11	-	8	-	4	-	1	-	16	-	5	-	1	-
Clindamycin	-	2	-	13	18	6	11	4	14	4	3	-	1	-	8	-	4	-	1	-	1	-
Nadifloxacin	25	17	6	10	11	2	8	-	7	-	2	-	2	-	-	-	-	-	-	-	-	-

PA: *Propionibacterium acnes*, MIC: Minimum inhibitory concentration, CNS: Coagulase-negative staphylococci

Table 5. Resistance rates of *P. acnes* and coagulase-negative staphylococci for the related antibiotics in the study

	Tetracycline		Erithromycin		Clindamycin		Nadifloxacin	
	Resistant	Intermediate*	Resistant	Intermediate	Resistant	Intermediate	Resistant	Intermediate
	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
P. acnes	0	0	0	0	0	0	0	0
CNS	28% (17)	0	36% (22)	18% (11)	23% (14)	5% (3)	0	3% (2)

P. acnes: *Propionibacterium acnes*, *Values between sensitive and resistant breakpoints

Informed Consent: Consent form was filled out by all participants.
Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.B., E.K., Concept: B.D., Design: B.D., Data Collection or Processing: B.D., B.B., E.K., M.Ö., Analysis or Interpretation: B.D., B.B., E.K., M.Ö., Literature Search: B.D., Writing: B.D.

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