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Clinical Efficacy of Topical Clindamycin Phosphate and Azelaic Acid on Acne Vulgaris and Emergence of Resistant Coagulase-Negative Staphylococci

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Abstract: In this study, the uses of topical clindamycin phosphate and azelaic acid were compared from point of clinical efficacy and emergence of resistant coagulase-negative staphylococci (CNS). Each group contained 20 patients. Pre- and post-treatment acne grades and comparison of two groups were evaluated by using the Wilcoxon and Spearman statistical techniques. The sensitivity of CNS to azelaic acid and to clindamycin phosphate were searched by microbroth dilution technique. Azelaic acid was found more effective in reducing acne grade. Eleven CNS strains were found resistant to clindamycin phosphate before treatment. After 8 weeks of therapy with topical clindamycin phosphate 18 of 20 CNS strains were resistant to this agent. No difference was detected for the MIC (minimal inhibitory concentration) values of CNS before and after topical azelaic acid treatment.

Key Words: Acne vulgaris treatment, clindamycin phosphate, azelaic acid.

Introduction

Acne vulgaris is the most common skin disease taking its origin from the pilosebaceous follicles. It affects nearly 80% of young adults, aged 11 to 30 years. It may cause disfiguration and permanent scarring and also it may have an adverse effect on psychological development, resulting in profound emotional scarring which may lead to social phobias, withdrawal from society, and clinical depression (1, 2, 3). The four main pathogenic factors in the development of acne are *increased sebum production, disorders of the microbial flora, cornification of the pilosebaceous duct, and inflammation* (1). For an effective treatment the drugs should be capable of influencing one or more of these factors in the pathogenesis of acne vulgaris.

The patients who have non-inflammatory comedones or mild to moderate acne are usually treated by topical agents. Azelaic acid and clindamycin phosphate are two of these drugs. The first one is a naturally occurring saturated C_9 dicarboxylic acid and a relatively new drug. The second agent is one of the most commonly used topical antibiotics in acne treatment (4, 5, 6).

Because of the widespread use of antibiotics in the treatment of acne, there has been increasing concern regarding the emergence of bacterial antibiotic resistance in the resident flora of the skin and gastrointestinal tract.

Systemic antibiotic therapy has been shown to be associated with an increase in multiple resistant CNS. This has potentially serious consequences for patients and their contacts. CNS have been found to be pathogenic in patients with indwelling catheters, in surgical patients, and in neonates. In addition, the ability of CNS to transfer resistance via plasmids to the more pathogenic *S. aureus* has been demonstrated. Information is scanty regarding the development of resistant staphylococci during treatment with topical antibiotics (7).

In this study we investigated the emergence of resistant CNS after 8 weeks of topical therapy with azelaic acid and clindamycin phosphate, and we compared their clinical efficacy.

Materials and Methods

1. Patients

This study was designed as a randomized and controlled trial. Patients were selected from the ones coming to The Hospital of Medical Faculty of Osmangazi University. The eligibility criteria for this study were being older than 18 or having the permission of the parents, having an acne grade less than or equal to 3.0 according to the Leeds' acne assessment technique (4). This technique has been reported to be a quick and

Table 1.   The result of patients who were treated with azeleic acid concerning age, sex and acne grade.

Patient number	Age	Sex	Acne grade		MIC (mol/L)	
			Pretreatment	Posttreatment	Pretreatment	Posttreatment
1	27	F	1.5	0.5	0.007	0.007
2	23	M	2.0	0.75	0.007	0.007
3	23	F	2.5	1.5	0.015	0.015
4	17	F	2.0	1.25	0.007	0.007
5	19	M	2.0	1.5	0.03	0.03
6	22	F	1.25	0.5	0.03	0.015
7	23	F	1.25	1.0	0.03	0.03
8	25	F	2.0	0.5	0.03	0.03
9	18	F	2.0	1.5	0.015	0.015
10	20	F	1.25	0.5	0.015	0.015
11	18	F	2.0	2.0	0.007	0.007
12	24	F	1.25	0.5	0.007	0.007
13	21	F	3.0	1.5	0.015	0.015
14	21	F	1.0	1.0	0.007	0.007
15	20	M	1.25	1.0	0.015	0.015
16	23	F	1.0	0.5	0.003	0.007
17	21	F	2.5	1.0	0.007	0.007
18	18	F	2.5	1.5	0.03	0.03
19	20	M	1.5	0.5	0.03	0.03
20	14	M	1.5	1.0	0.015	0.015

satisfactory method for clinical studies related with acne vulgaris. Pregnant or nursing women, the ones who had been using any acne treatment during the last month, the female patients who had taken estrogen preparations in the last three months were excluded from this study.

At the beginning of the study, each patient was informed about the treatment period and the possible adverse effects and written or oral consent was taken from the patient or his/her parents. The study was also permitted by the ethics committee of The Medical Faculty. The patients were applied either topical azelaic acid or topical clindamycin phosphate therapy until 20 patients for each group completed the study. The acne grade of each patient was noted at the beginning of the study according to the Leeds' technique (4). For this purpose, the patients were examined by inspection and palpation in a well-illuminated room. The patients whose acne grades were higher than 3.0 were not included in the study.

The differences between the ages, sexes, and the acne grades at the beginning of therapy in both patients groups were not statistically significant (Table 1-2) (Mann-Whitney-U Test, U=175.5; p>0.05).

At the end of therapy, the acne grades of the patients were assessed using the Leeds' technique. For both groups, the differences between the pre- and post-treatment acne grades and comparison of two groups were evaluated by using the Wilcoxon and Spearman statistical techniques.

2. Microbiological examination

The aforementioned drugs were applied to the patients twice daily for 8 weeks. Samples for bacteriological cultures were taken from the hairline, forehead and glabella at the beginning and at the end of 8 weeks. These samples were inoculated in the blood agar. After an overnight incubation at 35°C, the colonies which performed appropriate properties as morphology, Gram staining, and coagulase reactions were determined as CNS. The sensitivity of these CNS to azelaic acid and clindamycin phosphate were searched by microbroth dilution technique (9, 10). The 24 hours cultures of the CNS were adjusted to 0.5 Mc Farland turbidity (5×10^8 CFU/ml). Then these suspensions were diluted to 1:10 with distilled water. Ninety-four grams of azelaic acid was dissolved in 10 mol/L NaOH and 0.1 mol/L phosphate buffer and a stock solution was prepared in which had 0.5 mol/L azelaic acid in. Also 128 μg/ml clindamycin phosphate main solution was prepared. These stock

Table 2. The result of patients who were treated with clindamycin phosphate concerning age, sex and acne grade.

Patient number	Age	Sex	Acne grade		MIC (µg/mL)	
			Pretreatment	Posttreatment	Pretreatment	Posttreatment
1	27	F	1.5	1.0	8	8
2	21	F	2.0	1.5	4	4
3	18	F	1.25	1.0	0.5	4
4	26	F	2.0	1.5	2	4
5	19	M	2.5	2.0	8	16
6	21	F	1.0	1.0	4	8
7	25	F	3.0	2.5	0.5	4
8	21	M	1.25	1.0	4	8
9	20	F	2.5	2.0	0.5	4
10	21	F	1.25	1.25	0.5	0.5
11	23	M	2.0	1.5	0.5	4
12	19	F	1.5	0.75	4	8
13	21	M	1.0	1.0	8	8
14	18	F	1.5	1.0	8	8
15	25	F	1.25	1.25	0.5	4
16	22	M	2.0	2.0	0.5	4
17	24	F	1.0	0.5	4	4
18	19	F	2.0	1.5	16	32
19	22	M	1.5	0.5	4	4
20	23	F	1.0	0.75	2	2

solutions were diluted by two folds in Mueller Hinton Broth (dilution range: 0.5 to 0.003 mol/L, 128 to 0.12 µg/ml, respectively).

Microplates were incubated for 16 to 20 hours at 35°C. For the clindamycin phosphate group the MIC values equal to or more than 4µg/ml were accepted as resistant (10, 11).

Results

1. Clinical

The responses of the patients to the treatmet were measured by the decrease of the acne grade of each patient. The clinical improvement for both groups was found to be significant (Table 1 and 2) (T=0, p<0.01).

When the clinical improvement rates of the two groups were compared with each other, the clinical improvement in the azelaic acid group was found to be more significant than the clindamycin phosphate group.

Especially for the clindamycin group, side effects like erythema, burning, dryness, and peeling were noted in rare instances at the early days of therapy. These side effects were not the cause of cessation of therapy and almost entirely disappeared on the following days.

2. Microbiological

In the examination of the coagulase negative staphylococci isolated from the patients at the beginning of the study and at the end of 8 weeks, the following result were obtained:

a) In the azelaic acid group, the MIC values of the CNS were not observed to be significantly different beforeand after treatment (Table 1).

b) In the clindamycin phosphate group 11 CNS isolates were resistant to this drug before treatment. After 8 weeks of therapy with topical clindamycin phosphate, 18 of 20 CNS isolates were resistant to this drug. Eight of 20 CNS isolates presented no difference of MIC values before and after treatment. The other 12 strains, however, presented 2 to 8 times higher MIC values after therapy when compared with the MIC values before therapy (Table 2).

c) The species of CNS which were sensitive to clindamycin phosphate before treatment had higher MIC values after treatment.

Discussion

Acne vulgaris is one of the most common diseases seen in the dermatology clinics. Although it is not a life-

threatening disease it can seriously affect the quality of life (12, 13). During the last 20 years new data about the pathogenesis of acne has been recognized and by this mean a number of new drugs have entered to acne therapy. These drugs usually affect one or more of the four aforementioned pathogenic factors of acne (14, 15).

Antibiotics are commonly used in acne therapy. They are used topically or systemically. Tetracyline, clindamycin, and erythromycin are the mostly used antibiotics. These drugs also have anti-inflammatory effects besides their antimicrobial effects (4, 15). Azelaic acid is a naturally occurring dicarboxylic acid and a relatively new drug in acne therapy. It is reported that azelaic acid has a strong effect on microbial flora and a moderate effect on inflammation; thus it affects 2 of the 4 main factors in the pathogenesis (4).

In this study we planned to compare the efficacy of topical clindamycin phosphate and topical azelaic acid both clinically and microbiologically in acne therapy. Since both azelaic acid and clindamycin phosphate have antimicrobial effects, development of bacterial resistance is directly related with the therapeutic efficacy of these drugs. There are any studies which suggest that there is a significant development of resistance during the use of topical clindamycin but no reports have been yet written on this matter for azelaic acid (15, 16, 17). At the end of the study we found that both drugs were effective in the treatment of acne vulgaris, but azelaic acid was considered to be more effective in reducing acne grade.

The clindamycin resistance of the CNS showed an increase during the 8 weeks therapy with this drug whereas there was no difference in the azelaic acid resistance in the other group.

The better clinical results in the azelaic acid group may be due to no development of resistance to this drug and also the number of the affected pathogenic ways by these two drugs may be another factor. Clindamycin has only antibacterial and anti-inflammatory effects whereas azelaic acid has also an effect on follicular keratinization (4).

On the other hand CNS are the members of the normal skin flora and are the most common staphyloccocci species isolated from cutaneous sites. These microorganisms are easily shed from skin and may contaminate inanimate environmental surfaces, other people, and the air. CNS infections in surgical sites usual result from contamination by these organisms originating from the patient's skin or nasopharynx or coming from exogenous sources. Therefore colonization of resistant CNS strains may cause some problems in treatment of severe CNS infections (18).

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