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Evaluation of the Incidence of Anal Fissures in Patients who Systemic Isotretinoin Therapy for Acne

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ABSTRACT

Introduction: Isotretinoin is an effective drug widely used in the treatment of severe acne. In this study, we tried to evaluate the incidence of anal fissures with clinical and laboratory side effects associated with isotretinoin.

Methods: The study evaluated 210 patients who received systemic isotretinoin treatment. Especially patients with constipation and anal bleeding were evaluated by the General Surgery clinic to arrange appropriate treatments.

Results: Of 210 patients included in the study, 138 (65.7%) were female and 72 (34.3%) were male, with a mean age of 23.7 years. The most common adverse event was dry lips in 206 (98.1%) patients. The mucocutaneous side effects were constipation 36 (17.1%), anal bleeding 18 (8.6%), mucosal erosion 10 (4.7%), anal fissure 7 (3.3%). Treatment was discontinued due to elevated liver function tests in 5 patients (2.3%), and because anal bleeding could not be controlled in 1 patient.

Conclusions: Isotretinoin is the most effective acne medicine used today. Clarification of the patients about the rarely seen side effects such as dryness, erosion, fissure and bleeding in the anal mucosa in addition to the common mucocutaneous side effects will ensure that patients are more cautious and increase their tolerance to the treatment.

Introduction

Acne vulgaris is a multifactorial disease of the pilosebaceous unit that affects millions of people around the world to varying degrees. It affects about 85% of the young population. Although it is primarily a disease of the adolescent period, we observe it in neonatal and infancy periods, as well as prepubertal period and advanced age patients [1-3].

Primary pathogenic factors of acne are increased sebum production, changes in keratinization process, follicular colonization with the natural immune activation of Propionibacterium Acnes and increased inflammation. Lesions of various variations such as come done, papule, pustule, nodule and rarely cyst, characterize acne [4].

The distribution of acne lesions is often the face, back, chest and shoulder areas where sebaceous glands are densely located. Treatment of acne vulgaris varies based on the type, extent and severity of the lesions. While topical antibiotics and retinoid are the first choice in the treatment of mild acne, systemic antibiotics and anti-androgenic agents are used in moderate to severe acne [5,6].

The most effective treatment method for severe acne is systemic isotretinoin. Isotretinoin is an agent that suppresses sebum production and is effective on all pathogenic factors that play a role in the formation of acne and has been used in the USA since 1982 in the treatment of severe nodulocystic and persistent acne. However, as antibiotic resistance is increasing worldwide, antibiotic monotherapy has begun to be used less frequently in acne treatment. Classically used for nodulocystic acne, isotretinoin has become the drug of choice by dermatologists for moderate acne. It can also be used in seborrheic dermatitis, acne rosacea, and perioral dermatitis resistant to classical treatment [7-9]. Treatment protocol recommended in clinical applications is the use of 0.5-1 mg/kg/day over a period of 4-12 months to reach a total dose of 120-150 mg/kg [10]. The most common side effects observed during isotretinoin use are mucocutaneous side effects. Mucocutaneous side effects develop secondary to a decrease in sebum production, thinning of the stratum corneum and changes in skin barrier functions, among which the most common side effect observed is cheilitis. Almost all patients have cheilitis with varying severity. Other common side effects of systemic isotretinoin are nosebleeds, generalized muscle aches, malaise, and dry eyes. The most important side effect of the drug is its teratogenic effect [11,12].

Another system in which side effects of isotretinoin are seen is the gastrointestinal system (GIS). Regarding the side effects of GIS, Martin et al. have been the first to report a case of proctosigmoiditis in 1987. Afterwards, a few more cases have been reported on isotretinoin-related inflammatory bowel disease (IBD) [13,14].

Objectives

Isotretinoin can also dry the anal mucosa, triggering fissure formation. In this study, we evaluated the side effects and especially the development of anal fissures, mucosal damage and rectal bleeding in patients receiving systemic isotretinoin therapy.

Methods

The study included all patients who applied to dermatology clinic between 2018-2019 and received systemic isotretinoin therapy. The data were evaluated retrospectively (the local ethics committee confirmed that formal approval was not required for this retrospective audit of practice). Patients with missing data were excluded from the study. Participants were informed about the study. Adolescents who agreed to participate in the study provided signed informed consent forms.

Before treatment, all patients and their families were questioned for hyperlipidemia and atherosclerosis. Patients' demographic data such as age and gender as well as body weight, duration of the disease and the medications used were recorded. Before treatment, after treatment and at intervals during treatment, the following laboratory values were examined: hemoglobin, hematocrit, leukocyte, platelet count, erythrocyte sedimentation rate (ESR), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), cholesterol (low density cholesterol (LDL) high density cholesterol (HDL), very low density cholesterol (VLDL), triglyceride, creatine kinase (CK), and monthly beta-human chorionic gonadotropin (B-HCG) in female patients.

In the monthly follow-ups, all side effects were questioned in detail. Especially, patients with gastrointestinal system complaints were referred to the General Surgery clinic. The data of the patients, whose detailed examinations were performed here, were recorded on the follow-up form. The treatment of patients who could not tolerate side effects and had abnormal laboratory findings was terminated.

The data obtained were statistically analyzed using the software program SPSS 22.0. Continuous variables were expressed as mean ± standard deviation, and variables indicated by count were expressed as percentages. Chi-square tests were used in comparisons.

Results

Of 210 patients included in the study, 138 (65.7%) were female and 72 (34.3%) were male, with a mean age of 23.7 (16-59). Mean body weight of the patients was 62.1 (38-105) kg. The dose of isotretinoin ranged from 20 to 70 mg/day.

The treatment was regulated in such a way that 59.2% of our patients received 30 mg/kg/day and 36% received 40/mg/kg/day. The average duration of drug use by patients was detected to be 5.36 months.

The most common adverse event of isotretinoin was dry lips in 206 (98.1%) patients. Then, dry eye 87 (41.4%), nosebleed 73 (34.7%), muscle pain 58 (27.6%), malaise 56 (26.6%), facial erythema 39 (18.5%), itching 36 (17.1%), constipation 36 (17.1%), Xerosis 30 (14.2%), sun sensitivity 21 (10%), joint pain 17 (8.9%), anal bleeding 18 (8.6%), headache 18 (8.6%), hair loss 15 (7.1%), mucosal erosion 10 (4.7%), mental change 9 (4.2%), menstrual irregularity 8 (3.8%) and anal fissure 7 (3.3%) were observed, respectively (Table 1). No patient experienced abdominal pain. Five of the patients who developed anal fissure were female and 2 were male, and all had fissure with constipation and anal bleeding. Only 2 of 10 patients with mucosal erosion had constipation. In patients with fissure and mucosal erosion, the isotretinoin dose ranged from 30-70 mg/day. It was determined that 8 of 36 cases with constipation already had constipation before treatment. The comparison between gender and anal bleeding revealed that anal bleeding was more common in women (P = 0.029). In addition, no statistically significant difference was observed between gender and constipation (P = 0.226), drug dose given and constipation (P = 0.067), drug dose given and anal bleeding (P = 0.290) and drug dose given and fissure formation (P = 0.835). There was no history of IBD in patients or their families.

In 12 of the 210 patients (5.7%) enrolled in the study, elevations in liver function tests were identified, while 7 patients (3.3%) had triglycerides and 3 patients had high cholesterol (1.4%). Treatment was discontinued due to elevated liver function tests in 5 patients (2.3%), and because anal bleeding could not be controlled in 1 patient.

Patients with constipation and anal bleeding were examined in detail by the general surgery clinic. Medical treatment, topical moisturizers and appropriate diet were recommended to patients with fissure and mucosal erosion. The dose of isotretinoin was reduced in three patients. In the controls, symptoms were observed to improve except for one patient.

Table 1. Prevalence of adverse effects.

Adverse effect	Patients, N (%)
Dry lip	206 (98.1%)
Dry eyes	87 (41.4%)
Nose bleeds (epistaxis)	73 (34.7%)
Muscle aches (myalgias)	58 (27.6%)
Tiredness	56 (26.6%)
Facial erythema	39 (18.5%)
Itching of the skin	36 (17.1%)
Constipation	36 (17.1%)
Xerosis	30 (14.2%)
Sun sensitivity	21 (10%)
Headaches	18 (8.6%)
Anal bleeding	18 (8.6%)
Joint aches (arthralgias)	17 (8.1%)
Hair loss	15 (7.1%)
Mood change	9 (4.2%)
Heavy menstrual periods	8 (3.8%)
Anal fissure	7 (3.3%)
Herpes simplex	2 (1%)
Abdominal pain	0 (0%)

Conclusions

Acne vulgaris is a chronic inflammatory disease that primarily concerns adolescents. This condition, which affects 85% of people, is mostly seen in young girls and boys aged [15,16]. Acne vulgaris is treated with the use of topical treatments alone or topical and systemic treatments in combination, depending on the severity of the disease [5,6,16,17].

Isotretinoin, which is a synthetic retinoid, has been used for many years to treat nodulocystic acne. Today, it is used in the treatment of moderate to severe acne, severe seborrheic dermatitis, pyoderma faciale and gram-negative folliculitis, unresponsive to other treatments, including oral antibiotics. Isotretinoin is the only drug effective on all factors involved in the pathogenesis of acne vulgaris and is the most effective treatment tool in the treatment of acne vulgaris with a remission rate of up to 70%-89% [18-20].

The most common side effects related to the use of isotretinoin have mucocutaneous characteristics. Many of these symptoms are tolerable, treatable, and dose-dependent [19]. Cheilitis, dry nasal, dry eyes are the most common finding and occurs in almost all patients. Apart from these side effects, facial erythema, muscle aches, itching, malaise, joint pain and headache are other common side effects [21-25].

Many studies have been conducted on GIS side effects of systemic isotretinoin. First, Martin et al reported a case of isotretinoin-related proctosigmoiditis in 1987 [13]. Several other cases of isotretinoin-related IBD have been reported afterwards. This suggests that isotretinoin affects the intestinal mucosa [13,14,17,26]. Passier et al thought that three patients receiving isotretinoin with gastrointestinal system complaints might have IBD, and in the colonoscopy examination, ulcerative colitis was detected in two patients and Crohn disease in one [27].

However, in recent large-scale studies, no relationship between isotretinoin and IBD could be demonstrated [28-31]. Among the rarer GIS, side effects of isotretinoin include appendicitis, esophagitis, anorexia and weight loss [32].

Isotretinoin can affect the anal mucosa, and this can promote mucous dryness, leading to mucosal erosion and fissure formation. Anal fissure is a tear in the anoderm distal to the dentate line. The diagnosis of an anal fissure is made with the evaluation of the medical history, preferably on the proctology table, and basically through inspection. With a thorough assessment of pain in the anal fissure, diagnosis can be made with approximately 100% accuracy as early as at the stage of taking a medical history [33]. One of the most popular theories about anal fissure is that mucosal rupture and anal fissure develop after anal canal trauma secondary to constipation and hard stools. In addition, in patients with xerosis of the anal mucosa, hard stools due to constipation may traumatize the mucosa during the passage, causing fissure and pain and bleeding as a result [34,35].

Several cases of isotretinoin-related anal fissure and rectal bleeding have been reported in the literature [36,37]. In a study from our country, gastrointestinal side effects were detected in four patients (2.6%) [38]. In 1 of these, anal fissure developed in the first month of the treatment, rectal bleeding in the third month of treatment in 2 patients, and constipation in the fourth month of treatment in 1 patient. Other than these, several other cases with isotretinoin-related anal fissures and rectal bleeding have been reported in the literature [15,36,37]. Again, in different studies from our country and abroad [19,21,39], GIS side effects were found to be between 0.19%-0.3%. However, it has not been reported in detail whether these side effects are IBD or anal fissures. In our study, the number of patients with constipation was 36. Anal fissures were detected in 7 patients with constipation. Anal bleeding was another accompanying finding in all patients with fissure. However, constipation was detected in only 2 of 10 patients with mucosal erosion. This was a condition that supported isotretinoin causing dryness in the anal mucosa. Medical treatment and topical moisturizer were recommended by General Surgery clinic to patients complaining with fissure, rectal bleeding and constipation. In addition, the dose of isotretinoin was reduced in 3 patients. After treatment, there was an improvement in complaints in patients except for 1 patient.

In conclusion, frequent mucosal dryness in patients using systemic isotretinoin due to severe acne may also be encountered in the anal mucosa. Therefore, in addition to starting moisturizer to prevent cheilitis, dry eye and epistaxis in patients with whom we started isotretinoin treatment, topical moisturizers can also be added to the treatment of anal area dryness and an appropriate diet can be recommended. Presence of constipation and rectal bleeding should be investigated during patient controls. In the case of their presence, treatment should be arranged by the relevant clinics. Thus, possible fissure and severe mucosal erosion and subsequent rectal bleeding that may develop accordingly can be prevented. However, further case-controlled studies with low dose or fixed-dose are needed in order to clarify the relationship between systemic isotretinoin therapy and anal mucosal dryness, constipation, anal fissure, and rectal bleeding.

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