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The Effect of Isotretinoin-Induced Myalgia on Daily Quality of Life and Evaluation of Serum Creatine Phosphokinase Levels

İzotretinonin Kullanan Hastaların Miyalji Şiddet İndekslerinin ve Serum Kreatinin Fosfokinaz Düzeylerinin Değerlendirilmesi

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ABSTRACT

Objective: The aim of this study was to evaluate the effect of the myalgia observed as a side effect of isotretinoin used for severe and treatment-resistant moderate acne on patient quality of life and to investigate the relationship between serum creatine phosphokinase (CPK) levels and myalgia in these patients.
Materials and Methods: Two hundred and sixteen patients who are between the ages of 15 and 40 presenting to the outpatient clinic were included in the study. During isotretinoin treatment, the effect of muscle pain on the daily quality of life of patients with myalgia was evaluated according to the myalgia severity level (0:N/A; 1:Significant in the morning but not preventing normal activity during the day; 2:Affecting normal activity during the day; 3:Preventing normal daily activities). CPK levels of patients were screened retrospectively from their files.
Results: Of the 216 patients included in the study, 124 were female, 92 were male and the mean age was 24±5.3. Myalgia was detected in 48% of the patients (n: 104). Of the patients diagnosed with myalgia, 61.5% (n: 64) were classified as 1, 32.6% (n: 34) as 2 and 5.7% as 3. Serum CPK levels were elevated in 30.7% (n: 32) of the 104 myalgia patients.
Conclusion: Myalgia is a common side effect that can be seen in nearly half of patients during isotretinoin use. It was determined that the myalgia observed during isotretinoin use was at a tolerable level and had no significant effect on the daily quality of life. No correlation was found between myalgia and serum CPK levels.

Key Words: Isotretinoin, myalgia, creatine kinase

ÖZET

Amaç: Şiddetli veya tedaviye dirençli orta şiddetli akne tedavisinde kullanılan izotretinonin, yan etkileri arasında gözlenebilen miyaljinin günlük yaşam kalitesine etkisinin değerlendirilmesi ve bu hastalarda serum kreatin fosfokinaz (CPK) düzeyleri ile miyalji arasındaki ilişkinin araştırılması amaçlanmıştır.
Gereç ve Yöntem: Polikliniğe başvuran 15-40 yaş arası 216 hasta çalışmaya alınmıştır. İzotretinonin tedavisi sırasında miyalji tespit edilen hastaların kas ağrılarının günlük yaşam kalitesine etkisi değerlendirilmiştir. Değerlendirme 0: Yok, 1: Sabah kalkınca farkedilen ve gün içerisinde aktiviteleri engellemeyen, 2: Gün içerisinde normal aktiviteyi etkileyen, 3: Günlük aktivitelerin yapılmasını engelleyen şeklinde sınıflandırılmıştır. Çalışmaya alınan ve miyalji tespit edilen hastaların CPK düzeyleri ise retrospektif olarak dosyalarından taranmıştır.
Bulgular: Çalışmaya alınan 216 hastanın 124'ü kadın, 92'si erkek olup yaş ortalaması 24±5,3.'dir. Hastaların %47'sinde (n: 104) miyalji tespit edilmiştir. Kadın hastaların %55,7'sinde (n: 58), erkek hastaların %50'sinde (n: 46) miyalji mevcuttu. Miyalji tespit edilen hastalar değerlendirildiğinde 1: Sabah kalkınca farkedilen ve gün içerisinde aktiviteleri engellemeyen kas ağrısı %61,5 (n: 64), 2: Gün içerisinde normal aktiviteyi etkileyen kas ağrısı %32,6'sında (n: 34), 3: Günlük aktivitelerin yapılmasını engelleyen kas ağrısı %5,7 (n: 6) mevcuttu. Miyalji tespit edilen 104 hastanın %30,7'sinde (n: 32) serum CPK düzeyinde artış tespit edilmiştir.
Sonuç: İzotretinonin kullanımı sırasında miyalji hastalarının yarısına yakınında görülebilen sık bir yan etkidir. İzotretinonin kullanımı sırasında gözlenen miyaljinin tolere edilebilir düzeyde olduğu günlük yaşam kalitesine etkisi olmadığı saptanmıştır. Miyalji ile serum CPK düzeyi arasında korelasyon olmadığı tespit edilmiştir.

Anahtar Kelimeler: İzotretinonin, myalji, kreatin kinaz

Introduction

Isotretinoin is the best treatment option for severe and treatment-resistant moderate acne. It has been approved by the FDA for the treatment of acne since 1982 (1). Four major mechanisms are involved in the pathogenesis of acne formation: increase in sebum production, ductal keratinization, the development of microorganisms and inflammation. Isotretinoin effects all etiological factors in acne pathogenesis (2).

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There is a potential for broadside effects such as teratogenicity and laboratory changes and for systemic side effects affecting mucocutaneous, ophthalmological, musculoskeletal, gastrointestinal and mental health (3). Myalgia is among the toxic side effects of isotretinoin treatment (4). Isotretinoin has reportedly been associated with muscular adverse effects that most frequently manifest as myalgia and stiffness and, in rare cases, as true myopathy or rhabdomyolysis. Creatine phosphokinase, a specific marker of muscle destruction, has been found to be elevated, occasionally by up to 100 times the normal value (with or without muscular symptoms and signs), in a variable percentage of patients receiving isotretinoin treatment and particularly in those undergoing vigorous physical exercise (5,6). In this study, the aim was to determine the effects of myalgia on the daily quality of life of 216 patients who had reached a cumulative dose of 120-150 mg/kg and to evaluate the serum creatine phosphokinase levels of these patients

Material and Methods

The study was carried out at the Dermatology Polyclinic of Ağrı State Hospital between January 2014 and January 2016. Included in the study were 216 patients between the ages of 15 and 40 presenting to the outpatient clinic with moderate and severe acne who were treated with cumulative doses of 120-150 mg/kg isotretinoin. Patients with a history of hypo/hyperthyroidism, autoimmune disease, anticonvulsant or antidepressant drug use or a personal or family history of muscle disease and those previously treated with isotretinoin were excluded from the study. In this study, the effect of muscle pain on the quality of life of patients with myalgia during isotretinoin treatment was evaluated according to the myalgia severity level (0: no complaints about muscle pain 1: Significant in the morning but not preventing normal activity during the day; 2: Affecting normal activity during the day; 3: Preventing normal daily activities). Changes in the myalgia complaints according to the months were recorded in monthly follow-ups.

Serum creatine phosphokinase (CPK) levels were requested from patients with myalgia who had not exercised strenuously during the previous week and had no history of intramuscular injection. Serum creatine phosphokinase (CPK) levels of patients included in the study were screened retrospectively from their files. The values of patients with elevated serum CPK levels were evaluated in terms of multiples of the normal upper limit. Patients with a five-fold or greater increase in serum CPK levels were investigated for rhabdomyolysis in terms of urea-creatinine-electrolytes(calcium-phosphorous-potassium) via urine analyses.

Results

Of the 216 patients included in the study, 124 were female (mean age 23,4±5,3) and 92 were male (mean age 24,8±5,2). Myalgia was detected in 48% of the 216 patients (n: 104). Of those with myalgia, 55.7% (n: 58) were female and 50% (n: 46) were male. Of the patients diagnosed with myalgia, 61.5% (n: 64) were classified as 1 (muscle pain apparent in the morning but not preventing normal activity during the day), 32.6% (n: 34) as 2 (muscle pain affecting normal activity during the day) and 5.7% (n: 6) as 3 (muscle pain preventing normal daily activities). Serum CPK levels were elevated in 30.7% (n: 32) of the 104 patients with myalgia. Elevated serum CPK levels were found in 20.3% (n: 13) of patients presenting with myalgia 1, in 41% (n: 14) of patients with myalgia 2 and in 83.3% (n: 5) of the patients with myalgia 3. Levels were increased by two-fold in 10 patients, by three-fold in 15, by four-fold in four, by five-fold in two and by six-fold in one patient (Table 1).

In 64.4% (n: 67) of the patients, a history of onset of myalgia complaints was seen in the first month and in 35.6% (n: 37) in the second month of their treatment. The limitation of physical activity was experienced by 59.6% (n: 62) of the patients in the third month. In 27% of the patients (n: 28), complaints had completely regressed in the fourth month, while 10.5% (n: 11) of the patients were found to have a complaint of myalgia continuing throughout the treatment (Table 2). Three patients could not complete the treatment and the treatment of two patients was terminated according to their wishes. There was lack of regression of a six-fold elevation in the serum CPK levels of one patient and because the complaints of muscle pain affected his daily activities the treatment was terminated.

Discussion

Myalgia was observed in 61.5% of patients during isotretinoin use. It has been determined that myalgia does not restrict daily activities. Although CPK levels increased six-fold in two patients, rhabdomyolysis was not observed in these patients. Isotretinoin (13-cis-retinoic acid) is a vitamin A (retinol) analog. Retinoid drugs were first synthesized in 1955 and were first used in the treatment of psoriasis in Europe after 1973. In the United States, their use began after 1976 for the treatment of nodular acne that did not

Table 1. Relationship between serum CPK levels and myalgia

Myalgia Severity	Serum Creatine Phosphokinase Level				
	×2	×3	×4	×5 and above	Normal
1:61.5% (n = 64)	n:5	n:7	n:1	----	n:51
2:32.6% (n = 34)	n:4	n:7	n:3	----	n:20
3: 5.7% (n = 6)	n:1	n:1	----	n:3	n:1

Table 2. Time-related changes in myalgia during treatment

Myalgia Severity Level	Time of Myalgia Onset			Time of Myalgia Regression		Myalgia continued throughout treatment	Treatment terminated
	1st Month	2nd Month	3rd Month	3rd Month	4th Month		
1: (n=64)	39	25	----	45	15	4	----
2: (n=34)	24	10	----	17	12	5	----
3: (n=6)	4	2	----	----	1	2	3

respond to standard treatment (7). Isotretinoin has been approved by the FDA for the treatment of acne since 1982 (1) and is the only treatment agent that can act against all major etiological factors in the pathogenesis of acne. Although isotretinoin is known to reduce sebum release, comedone formation and *Propionibacterium* acnes colonization in the skin, as well as to exhibit anti-inflammatory activity, it is not clearly understood which mechanism or mechanisms are responsible for these effects. The side effects of isotretinoin, a first-generation synthetic vitamin A analog, are similar to those seen in excessive doses of vitamin A. The most important side effect is teratogenesis, while mucocutaneous side effects are the most common (7). Toxic side effects can include elevation of liver enzymes and blood lipid values, pseudotumor cerebri and muscle and bone pain (4). Brzezinski et al.(7) in the study with the largest series investigating the side effects of isotretinoin, covering 3525 patients, found lip dryness in 100% of the patients, nose bleeding in 47%, headache in 16%, joint pain in 12%, mood change in 6% and myalgia in 38.78% (n = 1367). Karadağ et al.(3) found myalgia in 45% of the patients in their study. Heudes and Laroche(8) reported myalgia in 51% of the patients and elevated serum CPK levels by 41%. In this study, myalgia was detected in 47% of 216 patients. Although there are studies in the literature evaluating the myalgia rate of patients using isotretinoin (3,7,8), no study had yet been carried out to investigate the effect of myalgia on the quality of life. In this study, the effect of myalgia on the quality of life was also evaluated. Of the patients who developed myalgia during isotretinoin use, 61.7% were affected in the morning, but normal activity during the day was not impaired, 32.6% of the patients carried out normal muscle activity during the day and 5.7% had muscle pain which prevented normal daily activities. Myalgia complaints became prominent at the end of the first month in 64.4% of the patients and at the end of the second month in 35.6%. In 86.5% of the patients who were recommended to limit exercise, there was a complete regression in the complaints after the 4th month, while in 10.5% of the patients, myalgia severity decreased and isotretinoin treatment was continued until completion. Treatment was discontinued in two patients because of muscle pain which prevented their daily activities, and in one patient because there was no regression in the serum CPK level and the muscle pain symptoms affected daily activities. Serum CPK levels were increased by 34.6% (n: 32) of the patients with myalgia. In three patients whose serum CPK levels (normal range 0-145 IU/L) had increased five times or more and who had muscle pain that prevented normal daily activities were investigated in terms of rhabdomyolysis. Urine tests were requested in order to evaluate urea-creatinine-electrolytes (calcium-phosphorus - potassium). As the results of the investigations revealed no pathological findings, rhabdomyolysis was not considered in these patients. In a study in which 89 patients were followed, Kaymak(9) reported that the elevation in serum CPK levels was non-specific because four of the five patients with elevated serum CPK levels were asymptomatic. Since the serum CPK levels were not examined in the non-myalgia group in the study, the evaluation could not be performed in terms of specificity. Landau et al. found elevated serum CPK levels in 165 (37.3%) of the patients and although the CPK level was higher than 5000 IU/L(15-167 IU/L) in seven of these patients, it was reported that no rhabdomyolysis was detected in

them (10). Heudes and Laroche (8) reported an increase in serum CPK in 41% of the patients in their study, and that five patients had a five-fold or greater increase in serum CPK was diagnosed with rhabdomyolysis. Patients presenting with rhabdomyolysis during isotretinoin treatment are also found in case reports where it was determined that rhabdomyolysis occurred in these patients after intense physical activity and it was emphasized that the physical activities of patients using isotretinoin should be limited (5,11-14). In our study, the finding of elevated serum CPK levels in 34.6% of patients presenting with myalgia is not directed at the myalgia but is suggestive that severe myalgia with a five-fold or greater increase in serum CPK may point to rhabdomyolysis if accompanied by muscle tenderness.

Myalgia is a common side effect that can be seen in nearly half of patients during isotretinoin use. The myalgia observed during isotretinoin use was at a tolerable level. Although no correlation was found between myalgia and serum CPK levels, patients with severe myalgia (elevated values of five times or higher) in particular should be investigated in terms of rhabdomyolysis.

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