Creatine phosphokinase values and myalgia during isotretinoin therapy

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Background: Systemic isotretinoin is a very effective medication for the treatment of acne, but it has some side effects. One of its side effects is musculoskeletal problems such as increased levels of creatine phosphokinase (CPK), myalgia, and serious muscle damage such as rhabdomyolysis. The aim of this study was to evaluate the incidence of myalgia and its relationship with the elevation of serum CPK levels in patients treated with isotretinoin.

Method: This study was done on forty acne patients in Razi Hospital. Isotretinoin was administered at a dose of 0.25 mg/kg in all patients. Serum CPK levels were measured before the treatment and every 2 months during treatment. On each visit, the patients were asked about muscular symptoms such as myalgia.

Result: Twenty-eight (70%) patients were female. The mean age of the patients was 22.6±5.4 years. The mean serum CPK level did not increase during treatment with isotretinoin. However, 2.5%, 36.8% and 31.5% of the patients had myalgia 2, 4, and 6 months after the initiation of isotretinoin, respectively. There was no significant difference in the mean CPK level of those who had myalgia after treatment with isotretinoin and those who were asymptomatic.

Conclusion: It seems that low dose isotretinoin does not induce the elevation of CPK, but can cause myalgia in some patients irrespective of the CPK level. Myalgia in patients under treatment with low dose isotretinoin is a benign phenomenon and is not an alarm for serious muscle damage. Therefore, routine measurement of the CPK level in patients receiving low dose isotretinoin is not recommended.

Keywords: acne, creatine phosphokinase, isotretinoin, myalgia

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INTRODUCTION

Acne is a very common skin disease, especially in adolescents and young adults. Various medicines are used to treat acne. One of these medicines is isotretinoin, which is a vitamin A derivative. Isotretinoin is a very effective treatment for acne and a number of other skin diseases which is ususally prescribed at a dose of 0.5-1 mg/kg orally. However, this medicine has known side effects. One of the side effects of isotretinoin is musculoskeletal problems manifested as myalgia, arthralgia, tendon and ligament calcification, premature closure of epiphysial plates, and decreased bone density. According to the literature, about 15-50% of the patients who receive isotretinoin have muscular complaints like myalgia [1-10]. Severe muscular damage and rhabdomyolysis have also been shown as rare side effects of isotretinoin [3,9,11]. Some studies have reported increased levels of creatine phosphokinase (CPK) following the administration of isotretinoin [11-13]. The serum levels of muscle

enzymes especially CPK, which are an index of the function of the muscular tissue, change in different physiologic and pathologic conditions. An increase in these enzymes may indicate cellular necrosis and tissue damage following acute and chronic muscular injury. Considering the fact that serum CPK levels can increase due to muscular injury, some studies have been conducted to evaluate the correlation of increased CPK levels with muscular complaints and serious muscular injury which have reported contradictory results. In the present rersearch, the serum levels of CPK during treatment and their correlation with muscular complaints in the patients receiving isotretinoin were investigated.

PATIENTS AND METHODS

Forty patients who were visitd in the dermatology clinic of Razi Hospital between October 2010 and February 2011 in whom isotretinoin was indicated were included in this study after signing an informed consent. The study protocol followed the guidelines of the decleration of Helsinki and was approved by the Ethics Committee of Tehran University of Medical Sciences.

Inclusion criterion was acne or other skin diseases for which systemic isotretinoin was indicated. Exclusion criteria were: 1) pregnancy or lactation, 2) childbearing age without reliable contraception, 3) history of hyperlipidemia, liver disease, muscular disease, cardiac disease or thyroid dysfunction, 4) concomitant use of other vitamin A derivatives, tetracyclin, statins, clofibrate and anticouaglants, 5) history of surgery, infection and fever during the last month, 6) exercise or receiving intrmuscular injection during 48 hours prior to blood sampling, and 7) alcohol use

All patients, except for one, received isotretinoin for moderate to severe acne. One patients received isotretinoin for dissecting cellulitis of the scalp. Isotretinoin was orally administered at a dose of 0.25 mg/kg in all patients. Serum CPK levels and other routine lab tests (liver enzymes including SGOT, SGPT, and alkaline phosphatase, and lipid profile) were evaluated on the first visit (before the start of the medicine), and then after every two months. On each visit, the patients were asked about muscular symptoms such as muscle weakness and pain. The patients were advised not to have intense physical activity 48 hours before blood sampling for CPK measurement. Finally, the prevalence of increased CPK and its correlation with muscular complaints was evaluated. SPSS v.19 was used for analysis. Mann-Whitney and repeated measure ANOVA were used to compare data. P values less than 0.05 were considered significant.

RESULTS

Twenty-eight patients (70%) were female and 12 patients (30%) were male. The mean (± SD) age of the patients was 22.6±5.4 years (range: 15-40 years) and their mean weight was 62.4±11.5 kg, ranging from 40 to 96 kg. The mean blood level of CPK was 108.1±73.1 IU/L before treatment (range: 42-425).

One of the patients did not return for follow-up two months after the start of the treatment; therefore, CPK was measured in 39 patients in the second month. Moreover, 2 patients in the 4^{th} month and 21 patients in the 6^{th} month were lost to follow-up. Therefore, CPK was measured in 38 and 19 patients in the 4^{th} and 6^{th} months, respectively. Table 1 shows the mean CPK of the patients in different time intervals and Table 2 presents mean CPK changes in different time intervals and their comparison. However, comparison of the CPK levels in different time intervals was made among the 18 patients who were visited every two months until the end of the 6-month period. According to Table 2, only the difference in the mean CPK level before and 2 months after the treatment was significant, which had a decreasing trend.

Among the 39 patients who were visited after two months of treatment for follow-up, 1 had mild myalgia (2.5%). Of the 38 and 19 patients who were visited for follow-up after 4 and 6 months of

Table 1. The mean, minimum, and maximum CPK levels in different time intervals

	Before treatment	2 months after treatment	4 months after treatment	6 months after treatment
mean	108.1	90.8	110.8	81.3
Standard deviation	73.1	41.3	95.5	35.1
minimum	42	39	36	41
maximum	425	200	580	175

treatment, 14 (36.8%) and 6 (31.5%) had myalgia, respectively. Table 3 shows the difference in the serum CPK between the patients who complained about myalgia in every visit and those who had no complaint. Of course this comparison was not possible after two months of therapy because only one patient had myalgia at that time.

DISCUSSION

In this study, we measured the serum CPK levels two, four, and six months after starting isotretinoin but observed no increase in the CPK levels. The CPK level even decreased two months after starting the treatment when compared to its level before the treatment. The mean level of CPK after four months was higher than its mean level after two months and a little higher than its mean level before treatment. The mean level of CPK again decreased six months after the start of the treatment. Interestingly, the mean CPK was the lowest six months after the start of the treatment (Table 1). Only the difference in the mean CPK level before and 2 months after the treatment was significant (p=0.02) which is not very noticeable because it had a decreasing trend. Overall, it could be concluded that treatment with isotretonoin did not increase the level of CPK in our patients (Table 2). Moderate myalgia was observed in one, 14, and 6 patients two, four, and six months after the start of the treatment, respectively. There was no significant difference in the mean CPK level of those who had myalgia after 4 and 6 months and those who were asymptomatic (Table 3). Considering the fact that a considerable number of patients developed myalgia 4 and 6 months after the start of treatment with isotretonoin (36.8% after 4 months and 31.5% after 6 months), it can be concluded that the administration of isotretinoin gradually causes myalgia in patients irrespective of the CPK levels.

Increased levels of CPK, myalgia, and rhabdomyolysis have been reported as the side effects of isotretinoin. In our study, a large number of patients developed myalgia after the administration of isotretinoin for some months but increased levels of CPK and rhabdomyolysis were not observed. In a study performed by Azizzadeh et al, in contrast to our study, the mean CPK level increased significantly in the end of the second, fourth, and sixth months of treatment with isotretinoin as compared to the pre-treatment level, but remained in the normal range. In this study, mild myalgia was observed in only 10% of the patients. This study concluded that increased CPK with or without muscular symptoms was a benign finding in patients who use isotretinoin and therefore did not recommend CPK measurement in patients with mild myalgia [14]. Lipinsky reported 7 patients on isotretinoin therapy who had increased CPK levels. The increase in CPK levels was severe in 4 and moderate in 3 patients but none of them had myalgia [13]. In a study performed by Bettoli in 1990, raised CPK was observed in 10 out of 63 patients who were receiving isotretinoin but only one of the patients with increased CPK had myalgia [5]. In another study conducted by Hull to evaluate the clinical side effects of isotretinoin in 189 patients between 1991 and 1996, isotretinoin was administered at a dose of 1 mg/kg. In this study, 30% of the patients developed back pain after a short time [15]. In another study by Heudes in 1998, of 60 acne patients who were receiving isotretinoin, 50% had myalgia and 70% had increased CPK levels.

Table 2. Comparison of mean CPK changes in different time intervals

	Mean CPK level		Mean CPK level	P value
Before treatment	133.2	2 months after treatment	94	0.02
		4 months after treatment	130.5	0.9
		6 months after treatment	81.6	0.05
2 months after treatment	94	4 months after treatment	130.5	0.22
		6 months after treatment	81.6	0.1
4 months after treatment	130.5	6 months after treatment	81.6	0.09

Table 3. Mean CPK levels in patients with and without myalgia

	Mean CPK levels in patients with myalgia	Mean CPK levels in patients without myalgia	P value
4 months after treatment	103 ± 74.9	115.3 ± 106.9	0.708
6 months after treatment	107.6 ± 49.5	69.1 ± 18	0.118

The level of CPK was five times higher than the normal range in 5 patients, which was diagnostic for rhabdomyolysis [3]. Landau performed a study on 242 patients receiving isotretinoin and reported that 7 patients had a substantial increase of 5000 IU/L or more in CPK but only 2 of them complaind about myalgia [12]. In another study conducted by Kaymak in 2008, of 89 patients receiving isotretinoin, 5 had CPK levels above the normal limits but only one of them had myalgia. In this study, the CPK changes were not investigated [2].

In the aforementioned studies, similar to our study, myalgia had no relationship with the increase in CPK. However, in contrast to our results, they reported increased CPK levels following isotretinoin administration. It seems that the major diference between our study and the studies which reported increased CPK levels and rhabdomyolysis is the dose of the administered isotretinoin. In the majority of the previous studies, isotretinoin was administered at a dose of 0.5-1 mg/kg versus 0.25 mg/kg in our study.

Numerous studies have shown the benefits of low dose (0.25 mg/kg) isotretinoin in the treatment of acne. Our study also showed that the administration of low dose isotretinoin decreased its serious side effects including rhabdomyolysis. Overall, it seems that the administration of isotretinoin at low doses does not increase the level of CPK, and the myalgia which is developed in patients receiving isotretinoin bears no relationship with the level of CPK. Therefore, routine measurement of the CPK level in patients receiving isotretinoin is not recommended. The limitations of this study include its small size and loss-to-follow-up of many patients in the 6th month.

REFERENCES

1. Sweetman S, editor. Martindale: The complete drug reference. 35th ed.London: Pharmaceutical Press; 2007.
2. Kaymak Y. Creatine phosphokinase values during isotretinoin treatment for acne. Int J Dermatol 2008;47:398-401.
3. Heudes AM, Laroche L. Muscular damage during isotretinoin treatment. Ann Dermatol Venereol 1998;125:94-7.
4. Tillman DM,White SI, Aitchinson TC. Isotretinoin, creatine kinase and exercise. Br J Dermatol 1990; 123(suppl 37):22-3.
5. Bettoli V, Tosti A, Capobianco C, Varotti C. Creatine kinase values during isotretinoin treatment. Dermatologica 1990;180:54-5.
6. Tripp TB, Abele DC. Creatine kinase levels and isotretinoin therapy. J Am Acad Dermatol 1986;14:130-2.
7. Koransky JS. Creatine phosphokinase levels and isotretinoin therapy. J Am Acad Dermatol 1987; 17(5 Pt 1):851-2.
8. McBurney EI, Rosen DA. Elevated creatine phosphokinase with isotretinoin. J Am Acad Dermatol 1984; 10: 528-9.
9. Trauner MA, Ruben BS. Isotretinoin induced rhabdomyolysis? a case report. Dermatol Online J 1999; 5:2.
10. Dicken CH. Retionoids: a review. J Am Acad Dermatol 1984; 11: 541-52.
11. Guttman-Yassky E, Hayek T, Muchnik L, et al. Acute rhabdomyolysis and myoglobinuria associated with isotretinoin treatment. Int J Dermatol 2003; 42: 499-500.
12. Landau M, Mesterman, R, Ophir J, et al. Clinical significance of markedly elevated serum creatine kinase levels in patients with acne on isotretinoin. Acta Derm Venereol 2001; 81: 350-2.
13. Lipinsky JT, Schwimmer B. Elevated CPK and isotretionoin. J Am Acad Dermatol 1985;12: 581-2.
14. Azizzadeh M, Yahyaee M, Ghorbani R. The effects of isotretinoin on serum levels of creatine phosphokinase and musculoskeletal symptoms in patients with acne vulgaris. Tehran Uni Med J 2011; 69: 309-14.
15. Hull PR, Demkiw-Bartel C. Isotretinoin use in acne: prospective evaluation of adverse events. J Cutan Med Surg 2000; 4: 66-70.