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Original Article

Adverse effects of systemic isotretinoin therapy: a study of 78 patients

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Abstract

Background Isotretinoin is an effective treatment for severe forms of acne refractory to other therapies, but it is a teratogen and can cause serious side effects. The side effects, in addition to the constitutional features are related to skin, mucosae, eyes, sexual organs, central nervous system, respiratory system and gastrointestinal tract. Deranged biochemical profile may also be seen in few patients.

Objective The current study was aimed to determine the frequency of side effects of systemic isotretinoin therapy in patients treated for acne, thereby assessing its safety.

Patients and methods During the calendar year 2004, all the acne patients attending the outpatient department of dermatology, Ziauddin Medical University, KDLB campus, Karachi, fulfilling the inclusion criteria, managed on systemic isotretinoin were enrolled. All were taking isotretinoin at a dose of 0.5mg/kg body weight daily. Baseline investigations were performed in all the patients i.e. liver function tests, lipid profile, complete blood picture and renal function tests. They were followed up for any side effects and clinical improvement. The baseline investigations were repeated monthly to see any biochemical and hematological derangements.

Results 78 patients, 42 females (53.8%) and 36 males (46.2%), with ages ranging from 18 to 24 years, were enrolled. 72 patients (92.2%, $p<0.001$) developed side effects with a variable frequency of at least one feature in each of these subjects. The side effects, in addition to the constitutional features, observed were related to skin (87.2%), mucosae (10.3%), central nervous system (5.2%), eyes (3.8%), reproductive organs (2.6%), respiratory system (1.3%) and gastrointestinal tract (1.3%). Deranged biochemical profile was also a feature in few patients (6.3%).

Conclusion The majority of the patients on systemic isotretinoin have side effects, the most common being cutaneous and mucosal but are trivial. Side effects pertaining to the other systems are less frequent.

Key words Isotretinoin, acne, depression, teratogenecity,

Introduction

Acne is a condition in which normally colorless, liquid sebaceous secretions are converted to solid white material. The skin responds to the trapped solid oil by turning red and swollen manifesting as comedones, papules, pustules, nodules, cysts and scarring. Various topical and systemic therapeutics are employed for the management of the disease.

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Isotretinoin is the only drug that can cure acne with no serious long-term side effects. The drug is an effective treatment for acne that is refractory to other therapies, but it is a teratogen and can cause serious side effects.[1,2] The side effects, which appear intermittently and are reversible is 7.2% of all the treated patients, can persist up to 12 years post-therapy.[2,3] A recent study from Israel showed that isotretinoin is far safer than many doctors think.[4] A three- or four-month course of isotretinoin damages the oil glands and markedly reduces the amount of oil that skin produces. The drug is administered typically for 4 to 6 months and then is withdrawn; yet, often the beneficial effects continue.

Some of the most common side effects are: dryness of the skin, lips, mouth, and lining of the nose. Other side effects, depending on the severity of acne, may include: facial or body rash, flaking of the skin, itching, peeling of palms and soles, increased sensitivity to sun, inflammation of the lips, mild nose bleed, bleeding and inflammation of the gums, easily injured skin and increased fatigue. Patients may experience some redness, dryness, or irritation of the eyes and variable amounts of hair loss. During the first few weeks of treatment, acne may get worse. Redness and itching of the affected skin are common initial effects. These should disappear as the therapy continues. FDA has received reports of depression, suicidal ideation, suicidal attempts, and suicide in patients treated with isotretinoin.[5]

The current study was aimed to determine the frequency of side effects of systemic isotretinoin therapy in patients treated for acne thereby assessing its safety.

Patients and methods

The current study was carried out in the outpatient department of Dermatology, Ziauddin Medical University, KDLB campus, Karachi, during the calendar year 2004. All the patients attending the out patient department managed on systemic isotretinoin fulfilling the inclusion criteria were enrolled. The enrolled subjects belonged to both sexes. Patients suffering from acne, requiring treatment for at least three months were included. Patients with mild to moderate acne receiving isotretinoin pulse therapy were not included. It was assured that the patients are not taking any other therapy simultaneously. Children and married ladies were ruled out, being not put on the therapy while only unmarried girls were managed. All the patients were taking isotretinoin at a dose of 0.5mg per kg of the body weight daily. Patients requiring a higher dose were also ruled out. The nature of therapy, its mode of action, merits and demerits were explained to the patients. Baseline investigations were performed in all the patients i.e. liver function tests, lipid profile, complete blood picture and renal function tests. All the patients being managed with isotretinoin were followed up weakly to look for any side effects and clinical improvement. The base line investigations were repeated monthly to see any biochemical and hematological derangement. The results were analyzed and tabulated.

Results

Seventy-eight patients, fulfilling the inclusion criteria were included in the study. There were 42 females (53.8%) and 36 smales (46.2%). The minimum age of

Table 1 Cutaneous side effects with isotretinoin therapy (n=78)

Side effects	*n (%)*
Acne flare	68 (87.2)
Cheilitis	67 (85.8)
Facial erythema	39 (50)
Xerosis	34 (43.5)
Pruritus	15 (19.2)
Thinning of hair	9 (11.5)
Desquamation of palms and soles	2 (2.5)
Edema	1 (1.3)
Onycholysis	1 (1.3)

Table 2 Mucosal and eye changes (n=78)

Side effects	*n (%)*
Dry oral mucosa	8 (10.3)
Epistaxis	4 (5.2)
Visual disturbances	3 (3.8)
Red eyes	2 (2.5)
Sore tongue	1 (1.3)
Watering from eyes	1 (1.3)

Table 3 Central nervous system findings (n=78)

Side effects	*n (%)*
Headache	4 (5.2)
Insomnia	2 (2.5)
Depression	1 (1.3)
Incoordination	1 (1.3)
Tinnitis	1 (1.3)
Dizziness	1 (1.3)

Table 4 Miscellaneous side effects (n=78)

Side effects	*n (%)*
Impotence	1 (1.3)
Impaired menses	1 (1.3)
Gastrointestinal tract	1 (1.3)
Respiratory system	1 (1.3)
Impaired LFTs	3 (3.8)
Impaired lipid levels	2 (2.5)

presentation was18 years and maximum 24 years (mean age 22 years). 72 patients (92.2%) developed side effects with a variable frequency of at least one feature in each of these subjects ($p<0.001$). The side effects, in addition to the constitutional features, observed were related to skin (**Table 1**), mucosae and eyes (**Table 2**), central nervous system (**Table 3**), reproductive organs, respiratory system and gastrointestinal tract (**Table 4**). Deranged biochemical profile was also a feature in few patients. The frequency of constitutional features was headache in 4 patients (5.2%), fatigue 3 (3.8%), fever 3 (3.8%) and weight loss in 1 patient (1.3%).

Discussion

Although, an effective treatment for acne, it has significant side effects on skin. Flare of the preexisting acne is a commonly reported side effect during the first week of therapy, however, it settles as the therapy progresses. It was observed in 68 patients (87.2%). Goulden *et al.*[2] and Al-Khawaja[6] have reported a comparable frequency of 94% and 99%, respectively, in their patients. Facial erythema was seen in 39 patients (50%). This finding is on agreement with the frequency reported by Goulden *et al.*[2] Other important side effects on skin had the following descending frequency: xerosis 34 patients (43.5%), pruritus 15 (19.2%), thinning of hair 9 (11.5%), desquamation of palms and soles 2 (2.5%), edema 1 (1.3%) and onycholysis in 1 patient (1.3%). The frequency of these findings in our study is comparable to the previous studies with minor variations.[2,7] A three- or four-month course of isotretinoin damages the sebaceous glands and markedly reduces the sebum secretion. Dry skin is associated with lack of water, which in turn is often associated with significant pruritus.[8]

Similarly, changes in mucosae and eyes have already been reported by different workers with variable frequencies.[2,7] Cheilitis is the most common manifestation and occurs in virtually all patients who receive systemic isotretinoin therapy. In fact, the absence of cheilitis in an apparent "Accutane failure" should raise the

suspicion of noncompliance.[8,9,10] This cheilitis generally requires continual application of topical emollients. Dry nasal mucosa accounts for nosebleeds in up to two thirds of patients during treatment, so lubrication to the anterior nares is required.

As far as constitutional features are concerned, Goulden *et al.*[2] and Bruno[7] have reported similar frequencies.

Patients taking the drug systemically or soon after stopping the therapy, have become depressed or develop other serious mental health problems.[5] Central nervous system changes have been reported in patients on systemic isotretinoin therapy but the frequency of such adverse effects in our study differs from the previous reports.[2,8] Headache, in our patients, was transient and settled as the therapy progressed; however, it may be an indication for underlying pseudotumor cerebri and a warning to stop the drug. All the other features were also transient. Depression needs a special mention as it may persist even after stopping the therapy. Further evaluation may be necessary, as no mechanism of action has been established for depression.[11,12,13]

Sexual dysfunction in the form of impotence has been reported previously.[2,7] These features were observed in both patients towards the end of therapy and settled as the therapy was discontinued. Gastrointestinal and respiratory side effects are uncommon.

Biochemical profile (liver function tests and lipid profile) was altered in 5 (6.3%) patients. Increased hepatic enzymes i.e. transaminases and alkaline phosphatase were observed after 2 months of therapy and did not warrant discontinuation of therapy. Goodman *et al.*[9] reported no significant difference in alkaline phosphatase. Tangrea *et al.*[14,15] have reported an increased serum transaminases in their patients on isotretinoin. Deranged lipid profile was a feature in 2 patients (2.5%), with increase in serum triglyceride, cholesterol, LDL level and a normal HDL. Al-Khawajah6 reported that elevation of plasma triglycerides levels was the most significant laboratory adverse effect. Gandola[12] reported increase in serum triglycerides (72%) and serum cholesterol (66%); however, the effect was reversible at the end of the treatment. In our patients, the deranged cholesterol and triglyceride profile was not severe enough to discontinue the therapy and returned to normal after the therapy was discontinued. Similar derangements in lipid profile have been reported by other workers.[2,6,7]

Teratogenecity was not observed in our study because only unmarried females were enrolled. However, these effects must be kept in mind while treating married ladies of child bearing age and making sure that two methods of contraception are employed simultaneously.[16]

Conclusion

Majority of the patients on systemic isotretinoin have side effects, the most common being cutaneous and mucosal but are trivial settle as the therapy progresses. Other systemic side effects are rare.

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