Toxicity of Low-Dose Intermittent Isotretinoin in Recalcitrant Acne

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Abstract

Background: Isotretinoin, an oral retinoid, has been utilized to achieve long term remissions in cases of recalcitrant acne. In the conventional dosage schedule, the use of oral isotretinoin has been limited by the occurrence of biochemical abnormalities such as hypertriglyceridaemia and impaired liver function tests and radiological changes consistent with diffuse idiopathic skeletal hyperostosis. Low-dose intermittent regimen of oral isotretinoin has been evolved as a cost effective alternative to the conventional dosage regimen in cases of acne. This study addresses the issue of adverse effects of low-dose intermittent isotretinoin and the safety of this regimen.

Methods: A total of 60 cases of recalcitrant acne were included in the study. Baseline haematological, biochemical and radiological investigations were carried out. Low-dose intermittent isotretinoin was instituted in a dose of 0.5 mg/kg/day for one week in every four weeks for six months. The investigations were repeated at the end of six months therapy.

Result: High triglyceride levels occurred in 5% of cases whereas impaired liver function tests and skeletal hyperostosis of the spine were not observed in any case after low-dose intermittent isotretinoin.

Conclusion: The low-dose intermittent regimen in cases of acne may be utilized to limit the systemic toxicity of oral isotretinoin.

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Key Words : Recalcitrant acne; Isotretinoin; Low-dose intermittent regimen

Introduction

The peak in incidence and severity of acne occurs in adolescence affecting 40% of females between 14-17 years of age and 35% of males between 16-19 years of age [1]. There has been a significant increase in the prevalence of adult acne in recent years [2]. The emergence of bacterial resistance of *Propionibacterium acnes* has resulted in an increase in the number of cases of treatment-resistant acne [3]. Acne is associated with considerable psychosocial morbidity and any assessment of severity must take into account the patients perception of the condition [4].

Cases of recalcitrant acne may be defined as those cases with <50% improvement after six months of oral and topical therapy, cases relapsing rapidly after discontinuation of therapy, cases with scarring and cases associated with psychological distress [2]. Oral isotretinoin (13 cis-retinoic acid) is an effective modality in the therapy of recalcitrant acne not responding to conventional therapy, even when administered in a low dose [5,6].

In the conventional dosage regimen, isotretinoin is administered in a dose of 0.5-1.0 mg/kg body weight up

to a total cumulative dose of 100-120 mg/kg, the course of therapy being 4-5 months. Patients given a total cumulative dose of 100-120 mg/kg are less likely to relapse [2]. However oral isotretinoin is associated with considerable systemic toxicity in the conventional dosage schedule [7].

The low-dose intermittent regimen consists of isotretinoin 0.5 mg/kg per day for one week in every four weeks for a total period of six months [2, 8]. The frequency and severity of mucocutaneous side effects were lower with low-dose intermittent regimen than with conventional isotretinoin therapy [9]. Data on the systemic toxicity of low-dose intermittent isotretinoin is limited.

The aim of this study is to evaluate haematological, biochemical and radiological abnormalities associated with low-dose intermittent isotretinoin therapy in cases of recalcitrant acne.

Material and Methods

The study was conducted at two tertiary care hospitals of the army from Aug 2005 to Jul 2007.

A total of 60 cases of recalcitrant acne (Table 1) in the study included not only those cases that were not responding

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to therapy or were relapsing after therapy, but also cases associated with scarring or psychosocial distress.

Age of the patients ranged between 12 to 47 years, highest frequency being in the 18-23 years age group (Table 2). Children below the age of 12 years were not included in the study due to the risk of systemic toxicity.

Of these, 31 (51.7%) patients were male, while 29 (48.3%) were female (Table 2). Married women in the reproductive age group were excluded from the ambit of the study due to the teratogenic effect of the drug, unless primary as well as secondary forms of contraception were adopted and pregnancy tests were negative. Effective contraception was adopted at least one month prior to starting isotretinoin and was continued for one month after its discontinuation.

The baseline haematological, biochemical and radiological investigations that were carried out included haemoglobin estimation (Hb), total and differential leukocyte counts (TLC, DLC), total bilirubin, serum glutamine pyruvate transaminase (SGOT, SGPT), total cholesterol, triglycerides (TGL), high density lipoproteins (HDL), low density lipoproteins (LDL) and radiograph of the lumbosacral spine.

All the patients were administered oral isotretinoin in the low-dose intermittent regimen of 0.5 mg/kg/day for one week in every four weeks for six months. The patients were followed up every four weeks. The investigations were repeated at the end of six months of therapy.

Patients who did not complete therapy or were lost to follow up have not been included in the study.

Results

Hb, TLC, DLC and platelet counts remained within the

Table 1
Cases of recalcitrant acne

Diagnosis	Number of cases
Acne vulgaris	29
Truncal acne	15
Nodulocystic acne	12
Acne with hidradenitis suppurativa	1
Acne with scarring	1
Acne with keloids	1
Acne with idiopathic hirsutism	1
Total	60

Table 2
Sample characteristics

Age in years	Number of patients		Total
	Male	Female	
12 – 17	9	10	19
18 – 23	15	12	27
24 – 29	3	1	4
30 – 35	2	4	6
36 – 41	1	1	2
42 – 47	1	1	2
Total	31 (51.7%)	29 (48.3%)	60

normal range in all patients after low-dose intermittent isotretinoin therapy. Leucopenia or increase in platelet counts after therapy was not observed in any case in this study.

Baseline level of biochemical parameters e.g. cholesterol, TGL and LDL may hypothetically increase, decrease or remain the same, at the end of therapy. Any increase in level of these parameters above normal would be significant and indicative of an adverse effect of therapy. In nearly all cases in this study, the level either increased or decreased after low-dose intermittent isotretinoin. In only one instance had the level remained the same.

The manner in which any change in a biochemical parameter after isotretinoin therapy was factored in is clarified in Table 3. In a particular case if the baseline level of a biochemical parameter was already high, it was factored in only if the level showed a further increase after therapy. If the level showed a decrease or remained the same it was not included.

Serum total bilirubin level remained within the normal range of 0.3-1.3 mg/dl after low-dose intermittent isotretinoin therapy in all cases. Though baseline SGOT level was marginally raised above the normal range of 12-38 IU/l in one case, there was no further increase after therapy. In all other cases SGOT level remained within normal limits. SGPT level remained within the normal range of 7-41 IU/l prior to and after isotretinoin therapy in all cases.

Baseline total cholesterol level was found to be borderline-high (200-239 mg/dl) in five patients and high (240 mg/dl and above) in one patient. The latter with baseline cholesterol level of 250 mg/dl was closely monitored and managed conservatively without discontinuation of isotretinoin.

Increase in cholesterol level from normal or raised baseline level to borderline-high level was observed in five (8.3%) patients and to high level in three (5%) patients after low-dose intermittent isotretinoin therapy (Table 4).

Serum TGL was borderline-high (150-199 mg/dl) in 13 patients and high (200-499 mg/dl) in two patients prior to low-dose intermittent isotretinoin therapy. The latter two cases with baseline TGL above 300 mg/dl prior to therapy were closely monitored and advised increased physical

Table 3
Inclusion of biochemical parameters

Baseline level	Post treatment level	Remarks
Normal	Normal	Not included
	Borderline high	Included
	High	Included
Borderline high	Normal	Not included
	Borderline high	Included if post treatment level higher than baseline level
	High	Included
High	Normal	Not included
	Borderline high	Not included
	High	Included if post treatment level higher than baseline level

Table 4

Increase in serum cholesterol from baseline levels to borderline-high or high levels after low-dose intermittent isotretinoin

	Number of cases (%)
Increase to borderline-high cholesterol levels	5 (8.3)
Increase to high cholesterol levels	3 (5)
Total	8 (13.3)

Table 5

Increase in triglyceride levels from baseline levels to borderline-high and high levels after low-dose intermittent isotretinoin

	Number of cases (%)
Increase to borderline-high triglyceride levels	12 (20)
Increase to high triglyceride levels	3 (5)
Total	15 (25)

activity and weight reduction with a low fat, low carbohydrate diet. In the first case, TGL increased from a baseline level of 312 mg/dl to 330 mg/dl after isotretinoin therapy. In the second case, TGL declined from a baseline level of 301 mg/dl to 280 mg/dl after isotretinoin therapy. An increase in TGL from normal/raised baseline level to borderline-high level was observed in 12 (20%) cases and to high level in three (5%) cases after low-dose intermittent isotretinoin therapy (Table 5).

A mild decrease in HDL to a level below 40 mg/dl from normal or low baseline level was observed in 22 (36%) patients after low-dose intermittent isotretinoin therapy. Baseline LDL were borderline-high (130-159 mg/dl) in four cases. Increase in LDL from normal or raised baseline level to borderline-high level occurred in six (10.0%) cases and to high level (160-189 mg/dl) in one (1.7%) case after low-dose intermittent isotretinoin therapy (Table 6).

Radiological examination of the lumbar spine was carried out before and at the end of low-dose intermittent isotretinoin therapy in all cases. Baseline radiological examination revealed unilateral sacralisation of fifth lumbar vertebrae in two patients and spina bifida in one patient, as incidental findings. However radiological findings consistent with diffuse idiopathic skeletal hyperostosis of the spine were not observed in any case after isotretinoin therapy.

Discussion

In this uncontrolled, open-label observational study the occurrence of haematological, biochemical and radiological abnormalities in 60 cases of recalcitrant acne treated with low-dose intermittent isotretinoin was evaluated.

In the initial trial of oral isotretinoin (13 *cis*-retinoic acid), its indisputable therapeutic effects were demonstrated with marked reduction in lesion counts in treatment-resistant cystic acne cases at the end of four months of treatment [7]. Isotretinoin, an oral retinoid,

Table 6

Increase in low density lipoproteins (LDL) from baseline levels to borderline-high and high levels after low-dose intermittent isotretinoin

	Number of cases (%)
Increase to borderline-high LDL levels	6 (10)
Increase to high LDL levels	1 (1.7)
Total	7 (11.7)

induces marked inhibition of sebum synthesis [10]. When oral isotretinoin was introduced its use was restricted to cases of severe nodulocystic acne. Its use has now expanded to treat cases with less severe acne that are not responding satisfactorily to conventional therapy, particularly when associated with scarring or psychological distress [1,11].

In conventional dosage, the use of oral isotretinoin has been limited not only by the occurrence of mucocutaneous adverse effects, teratogenicity and depression with suicidal ideation, but also by biochemical abnormalities such as impaired liver function and hyperlipidaemia [7]. Teratogenicity precludes the use of isotretinoin in women in the reproductive age group who are likely to conceive, unless primary contraceptive measures are instituted and pregnancy tests are negative [12]. A convincing link between isotretinoin use and depression has not been demonstrated [13].

The low-dose intermittent isotretinoin regimen was evolved as a low-cost alternative to the conventional dosage regimen in cases of adult acne, in an effort to limit the adverse effects of isotretinoin [2]. The regimen consists of isotretinoin, 0.5 mg/kg/day for one week in every four weeks for a total period of six months. The efficacy of the low-dose intermittent regimen in mild to severe acne has been established by various studies [8,9]. Various fixed low-dose regimens have also been evolved. Regimens with fixed low-dose isotretinoin 20 mg per day and 20 mg on alternate days for a total duration of six months have been found to be effective in moderate acne [6,14].

Transient impairment of liver function tests that return to pretreatment levels has been reported with the conventional dosage regimen and also with fixed low-dose isotretinoin [6,15]. However, the changes in tests of liver function may not be significant [15]. In this study, liver function tests including total bilirubin levels and transaminases, remained within normal limits after low-dose intermittent isotretinoin in all cases.

Hyperlipidaemia, with elevation in cholesterol and TGL has been reported with isotretinoin in conventional dosage [7]. Fixed low-dose isotretinoin has also been associated with elevated serum lipid levels [6]. Elevation in cholesterol levels may occur in 30% of cases after

isotretinoin in conventional dose [7]. In this study, though increase in cholesterol to borderline-high levels (200-239 mg/dl) was observed in 8.3% of cases, increase to high levels (240 mg/dl and above) was observed in only 5% of cases after low-dose intermittent isotretinoin.

Elevation in TGL levels has been reported in 50% of cases after conventional dosage isotretinoin [7]. TGL elevations during isotretinoin therapy may predict a risk of the metabolic syndrome later in life [16]. Elevation in TGL above 800-1000 mg/dl may precipitate pancreatitis [7]. In the present study, though an increase in TGL to borderline-high level (150-199 mg/dl) was observed in 20% of cases, increase to high TGL level (200-499 mg/dl) occurred in only 5% of cases after low-dose intermittent isotretinoin. In this study, increase in LDL to borderline-high level (130-159 mg/dl) occurred in 10% of cases and high level (160-189 mg/dl) in 1.7% of cases after low-dose intermittent isotretinoin.

Lipid elevations are reversible on cessation of therapy. Guidelines have been proposed for close monitoring if TGL exceeds 300 mg/dl or total cholesterol exceeds 250 mg/dl and discontinuation of isotretinoin therapy if TGL exceeds 400 mg/dl or total cholesterol exceeds 300 mg/dl [17]. Slight to moderate increases in TGL (300-500 mg/dl) during isotretinoin therapy are managed with weight reduction, increased physical activity and a low fat, low carbohydrate, low alcohol diet. For TGL levels above 500 mg/dl, addition of a lipid lowering agent or reduction in dose of isotretinoin are considered. Only when conservative and medical management fails, drug discontinuation is considered [7].

Haematological abnormalities such as leucopenia and increased platelet counts have been reported with isotretinoin in conventional dosage [7]. Close monitoring if TLC falls below 2500/cu mm and discontinuation of isotretinoin therapy if the count falls below 300/cu mm has been proposed [17]. However haematological changes such as leucopenia and increased platelet counts were not observed in any case after low-dose intermittent isotretinoin in the present study.

The potential of oral isotretinoin in conventional dosage to cause periosteal bone formation, hyperostosis resembling diffuse idiopathic skeletal hyperostosis (DISH) and premature epiphyseal closure is limited but disturbing [2,7]. If hyperostosis involves the posterior longitudinal ligament, cord-compression with neurological deficit may occur [18]. However a recent study evaluating bone marrow density and spinal hyperostosis after conventional dosage isotretinoin for 16-20 weeks in adolescents did not reveal any detrimental effects [19]. In this study, radiological changes consistent with diffuse interskeletal hyperostosis of the spine were not observed after low-dose

intermittent isotretinoin in any case. Data pertaining to low-dose intermittent regimen of isotretinoin for the treatment of recalcitrant acne is limited. Though the efficacy of this regimen has been established [2,8,9], adverse effects other than cheilitis have not been reported.

This study was undertaken to address the issue of adverse effects of isotretinoin in the low-dose intermittent regimen. Low-dose intermittent regimen in cases of recalcitrant acne may be utilized to minimize the systemic toxicity associated with isotretinoin in conventional dosage.

A limitation of the present study is that comparison of the adverse effects of isotretinoin in conventional dosage regimen with low-dose intermittent regimen has not been carried out in a controlled trial. Moreover, long term follow up of the patients for adverse effects has also not been carried out.

Conflicts of Interest

This study has been funded by research grants from the O/o DGAFMS.

Intellectual Contribution of Authors

Study Concept : Col A Kumar, Col VK Kumar

Drafting & Manuscript Revision : Col A Kumar

Statistical Analysis : Col A Kumar, Col VK Kumar

Study Supervision : Col VK Kumar

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