

Adverse Effects of Isotretinoin Therapy

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The clinical and laboratory toxic findings of ninety-four patients receiving systemic isotretinoin therapy for cystic acne are listed. A comparison of the toxicity for two different dosage schedules is made. Coexistent diseases such as ulcerative colitis, manic depression psychoses, Gilbert's disease and cluster headaches are unaffected by this systemic medication.

Isotretinoin (13-cis retinoic acid), a synthetic retinoid, recently became available for prescription use in the United States. In experimental studies this drug has been effective in acne as well as a variety of disorders of keratinization.¹⁻⁴

Prior to its licensure here, less than 600 patients had been evaluated nationwide; consequently, little information on human toxicity was available.

Peck and co-workers⁵ administered to seven

Further evaluation of clinical and laboratory toxic findings in 523 patients receiving a mean daily dose of 109 mg for one hundred fifty days revealed that side effects were not confined to the skin and mucous membranes. Less common side effects included musculoskeletal and gastrointestinal symptoms, hair thinning, lethargy, fatigue, and headache.² In various instances, the severity of a particular side effect has warranted a reduction in the dose of isotretinoin,⁶ or its discontinuation.⁷

Isotretinoin causes a significant dose-related decrease in sebum production within two weeks. Sebum production was maximally reduced to nearly 10 percent of the pretreatment value within one month of therapy when a daily dose of 1.0 mg/kg was employed.⁴ In a more recent investigation by Stewart et al,⁸ the rates of sebum secretion were measured in twenty patients with severe cystic acne who were treated with isotretinoin at 1.0 mg/kg

TABLE I Dosage Groups Receiving Isotretinoin

	Group I (High Dose)	Group II (Low Dose)
Dosage	0.75-1.21 mg/kg	0.10-.22mg/kg
No. of Patients	46	48
No. of Patients Completing Treatment	45	47
Sex ratio (M/F)	29/16	24/23

vided into two dosage groups: 0.75 to 1.21 mg/kg a day, and 0.10 to 0.22 mg/kg a day for sixteen weeks. A careful medical history was taken before and at predetermined intervals during therapy. All side effects and their time course were catalogued. Although many of our findings are in agreement with previous data, we wish to report our observations regarding the dose, severity, and time course relationship of various side effects; the unusual associated untoward reactions; and the lack of interference of isotretinoin on the course of various diseases observed in our patients. Ten adult patients with dermatologic disorders, who were not receiving isotretinoin, were questioned about complaints listed in Table III. No significant positive responses were elicited.

Case Reports

Ninety-four patients with moderate to severe cystic acne were randomly divided into two dosage groups. The dosage and sex ratio of each group are noted in Table I. Before institution of therapy, a medical history was obtained. The concurrent diseases occurring in both patient groups are listed in Table II. The female patients were advised to employ effective contraception techniques during the treatment program. Pretreatment blood studies, including liver function tests, fasting serum triglycerides, and fasting serum cholesterol levels were obtained. Each patient was instructed to make note of any unusual symptoms during treatment. Once isotretinoin therapy began, each patient was followed at two-week intervals for the first month, then at monthly intervals thereafter until completion of a sixteen-week course. At each visit all side effects were recorded, and repeat liver function tests, fasting serum triglycerides, and fasting serum cholesterol levels were obtained. Only two patients were maintained on an additional acne medication (tetracycline) for a two-week period after initiating therapy.

Results

Of the ninety-four patients in this study, ninety-two completed the sixteen-week course.

TABLE II Coexistent Disease in Patients Studied

Psoriasis (2)
Ulcerative colitis (1)
Atopic dermatitis (1)
Manic depression (1) ⁶
Gilbert's disease (1)
Cluster headaches (1)

Clinical Findings—Table III shows that a number of side effects commonly occurred within the first two weeks of therapy, and in many instances began within the first twenty-four to forty-eight hours. These early side effects included cheilitis, facial erythema, xerosis, minor nosebleeds, dry mucous membranes, dryness of scalp and hair, pruritus, conjunctivitis, and gastrointestinal symptoms. In addition, Table III shows that some side effects did not occur until one month or later in the course of therapy. These late side effects included musculoskeletal symptoms, fatigue, minor depression, insomnia, decreased libido, weight loss, palmoplantar desquamation, edema, and respiratory infections. (Those side effects which occurred only once in this study were not categorized as either early or late.) Although there was little difference in the occurrence rate of acne flares, cheilitis, facial erythema, xerosis, dry mucous membranes or minor nosebleeds in the two dosage groups, these symptoms appeared to occur consistently earlier in the higher dosage group.

One of the most common side effects was an acne flare, of varying severity, which occurred usually within two to three weeks of therapy. These flares appeared as a result of an exacerbation of pre-existing lesions, or the onset of de novo lesions. The flare appeared more intense in the higher dose group. After the initial flare, many patients in both groups noted improvement because subsequent cysts appeared to heal faster than earlier, and upon rupturing, the contents of newer cysts was less.

Aside from acne flares, the most common mucocutaneous side effects were cheilitis, facial erythema, xerosis, minor nosebleeds, and dry mucous membranes, including rectal and vaginal dryness and irritation. The cheilitis appeared more intense in the higher dose group. The incidence of minor nosebleeds in this study approached 50 percent, twice the previously reported incidence.³ These minor nosebleeds were detected as "blood specks" on the patients' handkerchiefs.

Musculoskeletal symptoms, which often in-

TABLE III Clinical Findings in Ninety-Two Patients Receiving Isotretinoin for Sixteen Weeks

Findings	% Incidence (Total)		% Incidence (M/F)		Average Onset	
	Group I	Group II	Group I	Group II	Group I	Group II
Acne flare*	91	94	90/94	100/87	1-4 wks	2-4 wks
Cheilitis, dry lips	87	83	83/88	75/91	5-7 days	1-2 wks
Facial erythema	69	51	77/57	58/44	1 wk	1 wk
Xerosis (excluding scalp)	62	51	67/57	50/52	1-2 wks	1-4 wks
Epistaxis, petechial	47	45	47/44	50/39	1 wk	1-4 wks
Dry mucous membranes	36	43	26/57	42/43	1 wk	1-4 wks
Musculoskeletal	36	17	53/25	17/17	1-2 mos	1 mo
Scalp and hair dryness	24	23	23/25	25/20	1-4 wks	2-4 wks
Fatigue	22	30	37/25	33/26	1-2 mos	1-2 mos
Pruritus	11	2	10/12	4/0	2 wks	4 wks
Headache	11	11	17/0	8/13	2-4 wks	2 wks
Depression	11	11	10/13	4/18	1 mo	1 mo
Visual disturbances	11	11	13/6	13/17	2-4 wks	4 wks
Depressed libido	9	2	7/13	0/4	1 mo	3 mos
Thinning of hair	7	4	7/6	4/4	2-4 wks	1-2 mos
Insomnia	7	15	3/13	13/17	1-2 mos	1-2 mos
Weight loss	7	0	10/0	0/0	2 mos	—
Conjunctivitis, eye irritation	4	2	6/0	0/4	1 wk	2 wks
Palmoplantar desquamation	4	2	3/6	4/0	1 mo	1 mo
Skin fragility	4	2	3/6	4/0	4 wks	1 wk
Incoordination	4	2	7/0	4/0	4 wks	1-2 wks
Slow wound healing	2	0	0/6	0/0	1 mo	—
Edema	2	0	3/0	0/0	2 mos	—
Dizziness	2	0	3/0	0/0	1 mo	—
Tinnitus	2	4	0/6	4/4	4 wks	1-4 wks
Abnormal menses	2	11	—/6	—/22	3 mos	2 mos
Impotence	2	0	3/—	0/—	3 mos	—
Sore tongue	2	0	3/0	0/0	1 mo	—
Respiratory infections	2	9	3/0	8/9	3 mos	2 mos
Watery eyes	2	2	3/0	0/4	3 mos	2 wks
Onycholysis	2	2	3/0	4/0	1 wk	3 days
Gastrointestinal disturbances	0	4	0/0	0/9	—	1-14 days

*"Flares" indicate slight worsening of the disorder. It is not certain whether this reaction is drug-induced or a continuation of the cyclical disease.

cluded stiff or aching joints as well as "backache," were seen in 36 percent of the patients in Group I, which was more than double that in the lower dose group. Of interest, during the second month of therapy, one male patient in Group I had an atraumatic hydroarthritis of the right knee joint which required needle aspiration drainage.

The incidence of fatigue approached 25 percent overall, which was greater than the previously reported 10 percent.⁵ The appearance of fatigue did not correlate with liver chemical abnormalities.

Only one patient in Group II discontinued therapy because of extreme fatigue and drowsiness.

Abnormal menses were recorded in six patients, 15 percent of the women in this study. These were reported as either a "late or skipped" menstrual period. One patient missed two consecutive menstrual periods. The frequency of this side effect was much higher in the present study than previously reported.

Double vision or blurry vision was seen in approximately 13 percent of patients in the study, greater

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TABLE IV Laboratory Findings in Ninety-Two Patients Receiving Isotretinoin for Sixteen Weeks

	% Incidence (Total)		% Incidence (M/F)	
	Group I	Group II	Group I	Group II
Elevated triglycerides	20	6	17/25	8/4
Elevated cholesterol	9	2	3/19	0/4
Elevated liver function tests	18	6	17/19	8/4

than previously reported.^{4,5} Of particular interest was a man in Group I whose therapy was discontinued after he developed 80 percent blindness (new onset) within two weeks of therapy. Subsequently, this patient was thought to have acquired an unrelated demyelinating disorder.

Insomnia and minor depression were each seen in approximately 10 percent of the patients. Weight loss from seven to twenty pounds during therapy was noted in three men in Group I.

In spite of seasonal respiratory infections in this population, these episodes occurred in about 5 percent of the patients. All patients tolerated these infections normally.

Three patients noted easy bruising, and only one reported slow healing time for wounds.

Gastrointestinal disturbances and conjunctivitis appeared very infrequently in our patient groups.

An unusual feature of these adverse reactions was their intermittency in spite of continued isotretinoin ingestion. In addition, all these side effects have been entirely reversible after discontinuation or completion of therapy. No significant effect was noted in any of the patients' coexistent diseases (Table III). In addition, two patients recovered normally from otolaryngologic surgery when the drug was discontinued two days prior to surgery to one week postoperatively.

Laboratory Findings—Table IV shows the laboratory findings in the two dosage groups. There was a 20 percent, 9 percent, and 18 percent incidence

of elevated serum triglycerides, serum cholesterol, and liver function tests, respectively, in Group I, while receiving therapy. The incidence of abnormal elevations in Group I was at least three-fold that observed in the lower dose group (Group II).

Comments

The data from the present study indicates that certain side effects tend to occur early in the course of isotretinoin therapy, while others appear later. The most common side effects observed were: acne flares, cheilitis, facial erythema, xerosis, minor nosebleeds, dry mucous membranes, and musculoskeletal symptoms.

A significant dose relationship was revealed in the incidence of musculoskeletal symptoms and the development of hyperlipidemia. In addition, seven different side effects recorded in the higher dosage group did not appear in the patients receiving lower doses—suggesting dose-related symptomology.

Most side effects to isotretinoin can appear intermittently and are reversible. Only rarely do these adverse effects warrant discontinuation of therapy. Finally, no other concurrent disease adversely affected by this drug was detected.

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