

Evaluation of clinical adverse effects and laboratory alterations in patients with acne vulgaris treated with oral isotretinoin

Avaliação dos efeitos adversos clínicos e alterações laboratoriais em pacientes com acne vulgar tratadas com isotretinoína oral

Maria de Fátima de Medeiros Brito¹

Iara Pessoa Sant'Anna²

Juliana Cordeiro Souza Galindo³

Lígia Helena Pessoa de Melo Rosendo⁴

Josemir Belo dos Santos⁵

Abstract: BACKGROUND: Oral isotretinoin therapy has completely changed the treatment of acne. The clinical adverse effects of isotretinoin are classified into two groups: mucocutaneous and systemic toxic. Laboratory alterations such as dyslipidemia and increase of hepatic enzymes are reported.

OBJECTIVES: To evaluate the tolerability of oral isotretinoin with special attention to lipid metabolism, hepatic function, and clinical adverse reactions.

METHODS: 150 patients clinically diagnosed with acne being treated with oral isotretinoin were included in the study. Clinical and laboratory evaluations were conducted before the start of therapy, one month after, and every three months thereafter until the completion of treatment.

RESULTS: Of the 150 patients evaluated, 48% were female and 52%, male. They were aged from 15 to 32 years. The most prevalent mucocutaneous adverse reaction associated with isotretinoin therapy was cheilitis, reported by 94% of the patients. Systemic clinical effects were much less common. Cholesterol, triglyceride, and transaminase levels were assessed and significant changes were not observed during treatment.

CONCLUSION: Patients showed adverse effects compatible to those described in the literature, which are mostly controlled with symptomatic medication. Isotretinoin is a safe drug and adverse and laboratory effects are well tolerated.

Keywords: Acne vulgaris; Isotretinoin; Isotretinoin/ adverse effects

Resumo: FUNDAMENTOS: A isotretinoína oral revolucionou o manejo da acne. Os efeitos adversos observados, durante o tratamento, são divididos em dois grupos: mucocutâneos e sistêmicos. Anormalidades laboratoriais, principalmente, as dislipidemias e aumento das enzimas hepáticas são relatados.

OBJETIVO: Avaliar a tolerabilidade da isotretinoína oral, com atenção, no metabolismo lipídico, função hepática e reações adversas clínicas.

MÉTODOS: Foram incluídos 150 pacientes com diagnóstico clínico de acne submetidos a tratamento com isotretinoína oral. Avaliações clínicas e laboratoriais foram feitas, após um mês e a cada três meses, até completar o tratamento.

RESULTADOS: Dos 150 pacientes 48% eram do sexo feminino e 52% do sexo masculino. A idade variou de 15 a 32 anos. Quanto aos efeitos adversos cutâneos e mucosos da isotretinoína, queilite foi o mais frequente, ocorrendo em 94% pacientes. Efeitos clínicos sistêmicos foram bem menos comuns. Os níveis de colesterol, triglicérides, transaminases, foram avaliados e não mostraram alterações significativas, ao longo do tratamento.

CONCLUSÃO: Os pacientes apresentaram efeitos adversos, compatíveis com os da literatura, e, em sua maioria, controlados com medicações sintomáticas. Podemos concluir que a isotretinoína é uma droga segura, em relação a seus efeitos adversos, tanto clínicos como laboratoriais.

Palavras-chave: Acne vulgar; Isotretinoína; Isotretinoína/efeitos adversos

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¹ Ph.D. and M.S. in Tropical Medicine - area of concentration/major: Dermatology - Federal University of Pernambuco (UFPE) - Recife (PE), Brazil.

² Adjunct Professor at the Federal University of Pernambuco (UFPE) and Dermatologist at the University of Pernambuco/ Amaury de Medeiros Integrated Health Center (UPE/CISAM) - Recife (PE), Brazil.

³ Adjunct Professor at the Federal University of Pernambuco - Recife (PE), Brazil.

⁴ Post-graduate student in Dermatology at the Federal University of Pernambuco (UFPE) - Recife (PE), Brazil.

⁵ Professor and Head of the Dermatology Service at the Federal University of Pernambuco (UFPE) - Recife (PE), Brazil.

INTRODUCTION

Acne is a chronic inflammatory disease of the pilosebaceous unit, often self-limited, and it affects most commonly adolescents. It is clinically characterized by the formation of comedones, erythematous papules, pustules and, less frequently, nodules or pseudocysts.¹ Conventional topical and systemic treatment options are effective and improve lesions, but treatment with oral isotretinoin revolutionized the management of severe and resistant acne. Oral isotretinoin may lead to long remission or even permanent cure.^{1,2}

Isotretinoin is a type of retinoid that, since its introduction 25 years ago, has been widely used in the topical and systemic treatment of various dermatoses: psoriasis, keratinization disorders, keratotic genodermatosis, and severe acne. It is also used in the treatment and/or chemoprevention of skin cancer and other neoplasms. Retinoids influence the growth and differentiation of epidermal cells and interfere with sebaceous glands activity. Moreover, they have immunomodulator and anti-inflammatory properties.³

Retinoids are synthetic derivatives of vitamin A (retinol) and are important in the treatment of acne because they act on the primary lesion - the microcomedone -⁴ and aid in sebaceous suppression.

Conventional indications for treatment with oral isotretinoin include nodular-cystic acne and acne that is resistant to conventional treatment. The daily dose is calculated based on the patient's weight and varies between 0.5 to 1.0 mg/kg. To prevent relapses, a cumulative dose between 100 and 150 mg/kg is recommended. Cost of treatment and adverse reactions are still limiting factors to the use of isotretinoin by doctors and patients.⁵

The clinical adverse effects of isotretinoin, as well as those of other retinoids, are divided into two groups: mucocutaneous and systemic toxic effects.

Changes in mucous membranes and skin are due to a reduction in sebum production, thinning of the stratum corneum, and alterations in the skin barrier function.³ Most patients develop dryness and cracks (fissures) on the lips, skin, and mucosae. Lip dryness occurs in 100% of the cases and cheilitis, in 95%; these symptoms can be observed within the first 10 days of treatment.⁶ They are often controlled with lip moisturizers and antibiotics or antifungal medication, if necessary. Dryness of the nasal (50%) and oral mucosa (40%) is also common.⁶ Epistaxis occurs in approximately 30% of the cases.⁶ Dry eyes and blepharoconjunctivitis appear in 25% of the patients and are controlled with eye lubricants.⁶ Asteatotic dermatitis, pruritus, and scaly skin are frequent (25%). Digital fissures may occur.⁶ Photosensitivity occurs in 40% of the cases and is due to a reduction in the stratum corneum layers. Telogen effluvium may affect up

to 25% of the patients, disappearing after the end of treatment. Skin infections caused by *S. aureus* may develop due to an increase in its colonization resulting from a reduction in sebum production.⁷ Dermatitis may worsen in atopic patients. Nail fragility, periungual pyogenic granuloma, and paronychia are observed.³

The systemic toxicity of retinoids may affect muscles, bones, gastrointestinal tract, central nervous system, eyes, ears, thyroid, and kidneys. Bone alterations were first observed in patients treated for a long time for keratinization disorders. Bone pain without sequelae is often seen during treatment with retinoids. The long-term use of isotretinoin by patients with acne usually does not cause serious bone alterations - most are asymptomatic and insignificant hyperostosis.⁸ Osteoporosis has been observed with hypervitaminosis A and after a long treatment with etretinate, but not with isotretinoin.⁹ However, Leachman et al. (1999) showed loss of bone density (4.4%) without calcium level changes in patients after six months of isotretinoin use compared with a control group.¹⁰ Myalgias might occur, especially in patients who practice rigorous physical activity. Sometimes they are accompanied by an increase in creatine phosphokinase (CPK).¹¹ Effects on the central nervous system are rare. Individual signs of intracranial hypertension such as nausea, headache, and vomiting are occasionally observed. Pseudotumor cerebri syndrome is rare and one of its risks is the association of isotretinoin with tetracycline and its derivatives.^{3,12} A causal relationship between treatment with isotretinoin and depression, psychosis or suicide has been suggested, but there are doubts about this association.¹³⁻¹⁵ Eye dryness may occur, in addition to the following symptoms: alteration of visual acuity, night vision reduction, and changes in the perception of colors.^{16,17} Constipation may be a gastrointestinal effect. There have been reports of aggravation of intestinal inflammatory disease during treatment with retinoids.¹⁷ Pancreatitis and hypothyroidism are more associated with other retinoids. Hematologic toxicity is more frequently observed with the use of bexarotene and there are few case reports related to isotretinoin.¹⁸ Allergic reactions such as urticaria, polymorphous erythema, and pityriasis rosea-like eruptions have been described, but are not common. Laboratory alterations due to hepatic and hematologic toxicity, as well as dyslipidemias, should also be evaluated. Statistically insignificant, discreet elevations in the results of these tests occur with almost all patients, but levels return to normal after the drug has been suspended.^{1,5}

Serum measurements of hepatic and lipid

enzyme levels are considered routine procedure by most doctors at the start of and during treatment;¹⁹ however, the frequency of rigorous laboratory monitoring decreased throughout the past 20 years. Currently, the diligent use of contraceptive methods has been emphasized due to the teratogenic effects of this drug.²⁰ Recent studies show that there is no need for laboratory follow-up in patients undergoing treatment with oral isotretinoin.^{19,10,21,22,23}

Greater emphasis has been placed on the increase of triglyceride levels,²⁰ but studies show variable data: there is report of GOT (glutamic oxalacetic transaminase) increase in about 6% of the cases and of GPT (glutamic pyruvic transaminase), in 2.5%; of total cholesterol, in 14%, and of triglycerides, in 5%.²¹ Another study revealed that only 1.5% of the patients had triglyceride levels above 400mg%.¹⁹

The psychosocial impact suffered by patients with severe acne and scarring makes the establishment of an early, safe, and efficient treatment to improve their quality of life paramount.

Even though isotretinoin is a reasonably safe drug in relation to adverse reactions when the patient is well monitored, there is still resistance on the part of a few doctors to use isotretinoin to treat milder cases of acne that are irresponsive to conventional therapies. The objective of this study is to evaluate the frequency of clinical adverse reactions secondary to the use of isotretinoin in patients with acne vulgaris. The severity and intensity of these reactions will also be addressed, in addition to the frequency of laboratory alterations and the impact of these alterations in the treatment of patients.

MATERIALS AND METHODS

This is a study of a series of cases in which 150 patients with clinical diagnosis of acne being treated with oral isotretinoin were included. These patients were monitored at the ambulatory of Dermatology at Amauri de Medeiros Integrated Health Center (CISAM), Recife/Brazil.

Patients were examined periodically; clinical and laboratory evaluations were conducted before treatment, one month after the start of therapy, and every three months thereafter until completion of treatment. During the appointment sessions, questionnaires formulated specifically for the research were answered. Patients with fewer than four monthly appointments during treatment and those that missed the post-treatment follow-up were excluded from the study. The average dose of isotretinoin was 120 mg/kg, adjusted according to body weight and clinical evolution, varying between 0.5 and 1 mg/kg/day.

Data collection was accomplished through a review of the questionnaires, which had been filled out

by assistant physicians in the appointment sessions during treatment, included in the patients' medical charts. Prevalence, incidence, average, and standard deviation calculations were used in the analysis of the variables. Excel 2000 was employed in data processing.

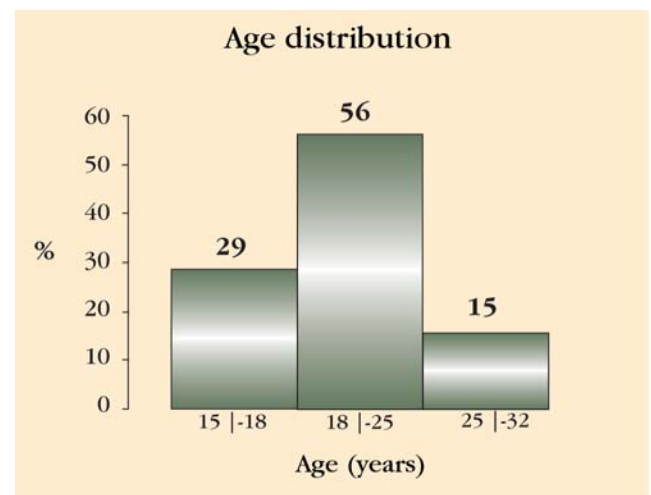
RESULTS

Of the 150 patients studied, 72 (48%) were female and 78 (52%), male. Patients were aged from 15 to 32 years; 29% were under 18 years old, 56% were between 18 and 25 years old, and 15% were over 25 years old (Graph 1).

Cheilitis was the most frequent cutaneous mucosal side effect of isotretinoin – it occurred in 141 (94%) patients. Xerodermia affected 71 (47.3%) patients and dryness of mucosae, 70 (46.7%). Palmoplantar scaling occurred in 31 (20.7%) cases, epistaxis, in 32 (21.3%), blepharoconjunctivitis, in 48 (32%), alopecia, in 34 (22.7%), nail fragility, in 38 (25.3%), and pyogenic granuloma, in 20 (13.3%). Pyodermitis occurred in 29 (19.3%) patients: 13 cases of furuncles, 9 cases of folliculitis, and 6 cases of impetigo. Flare-ups occurred in 9 (6%) patients (Graph 2).

Systemic effects were much less common. Osteomuscular pain was the most frequent, occurring in 17 (11.3%) patients, followed by headache in 14 (9.3%). Hearing complaints were reported by 2 (1.3%) patients. Tachycardia occurred in 1 case (Graph 2). There were no reports of other clinical or psychiatric systemic effects.

Cholesterol, triglyceride, transaminase, and alkaline phosphatase levels were evaluated before the start of treatment and twice later during treatment. Despite the fact that they showed some variation, it was not significant (Table 1 and graph 3).



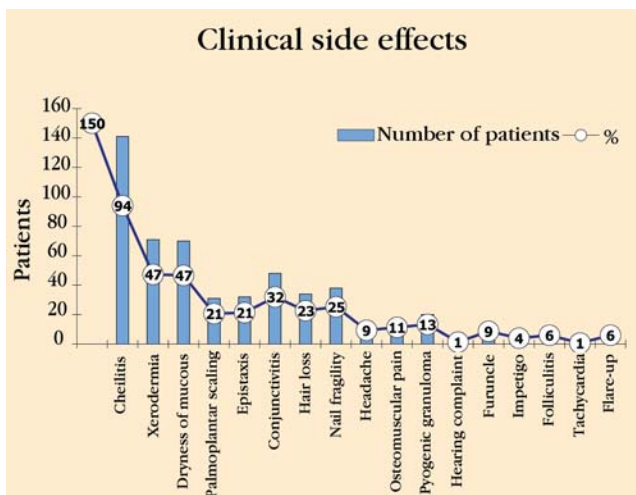
GRAPH 1: Age distribution of patients with acne treated with oral isotretinoin at CISAM, Recife- PE

DISCUSSION

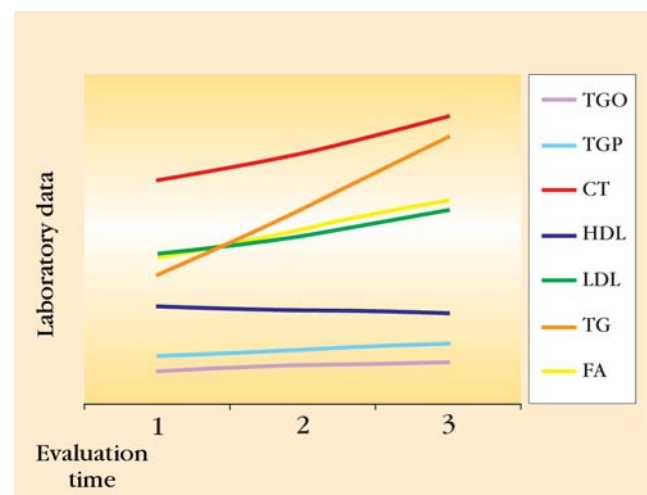
There were no significant differences in relation to gender distribution. The age distribution showed that most patients were between 18 and 25 years old (56%). Acne is a pathology that develops typically during puberty and adolescence, so the fact that most patients evaluated in this research were older than 18 years may be explained by unsuccessful early treatment attempts and by the fact that these patients come from the Brazilian Public Health System, where access to specialized health centers is difficult and isotretinoin is given free of cost only to those patients with level 3 or 4 acne. In addition, lack of information about isotretinoin and fear of its side effects may also have led to a delay in the start of treatment by the patients studied.

The frequency of mucocutaneous side effects was similar to that found in the literature. Cheilitis occurred in 94% of the cases, being similar to the frequency described by Sampaio in 2001. Some authors describe cheilitis in 100% of the patients as a marker of the action of the drug.¹⁸ Xeroderma and dryness of mucous membranes were reported in 47% of the cases, which is also compatible with data from the literature.⁶ As described in the introduction to this work, we can note that the frequency of other mucocutaneous effects shown by the patients was similar to that found in the literature. None of the effects mentioned were a reason to suspend the drug. Symptoms were controlled with lip balm and body moisturizers, eye drops, ophthalmologic evaluation and orientation. Patients with pyodermitis did not have to suspend the drug, either. Pyogenic granuloma occurred in 13% of the cases. The exact incidence of pyogenic granuloma or granuloma-like reactions secondary to the use of isotretinoin is unknown.²⁴ Report of three cases of granuloma-like reactions in 66 patients

(4.5%) treated with isotretinoin for nodule-cystic acne was found. These patients developed pyogenic granuloma-like reactions, inflammatory and hemorrhagic, in previous lesions of acne, which led to the suspension of the drug in two of them and to the use of prednisone by all of them.²⁴ The cases we studied were not so severe, so suspension of therapy was not necessary. Perhaps the percentage we obtained (13%) is higher because less severe cases and those that affected both acne lesions and other areas were considered. There were no reports of allergic reactions such as urticaria, polymorphous erythema or pityriasis rosea-like eruption. Systemic effects occurred in very few cases. There were 14 cases of headache, but none of intracranial hypertension syndrome. Headache was not a reason to suspend the drug in any of the cases. Despite the 48 cases of blepharoconjunctivitis, there were no other visual complaints such as loss of night or color vision or other visual acuity alterations. Two patients reported hearing problems not specified in the questionnaires. There are no reports about the frequency of hypoacusis or dysacusis with the use of isotretinoin. Deterioration in hearing acuity has been reported with the use of the drug and the symptom does not disappear after its suspension.¹⁷ The mechanism that causes this impairment is unknown and patients must be referred to an otorhinolaryngologist for evaluation.¹⁷ There was no description of the type of hearing complaint or its severity in the data collected for the research; however, they were not a reason to suspend the drug, and this suggests that causes for the complaints were not so severe. Osteomuscular pain was reported by 11.3% of the patients. Arthralgias and myalgias occur in retinoid users, particularly if they practice intense physical activity. In



GRAPH 2: Distribution of clinical side effects presented by patients with acne treated with oral isotretinoin at CISAM, Recife-PE



GRAPH 3: Evolution of the laboratory data of patients with acne treated with oral isotretinoin at CISAM, Recife-PE

TABLE 1: Mean and standard deviation distribution of laboratory exams of patients with acne treated with oral isotretinoin at CISAM, Recife-PE

Laboratory Exams	(Mean ± SD)	
GOT	23,26	2,73
GPT	21,79	2,60
Total cholesterol	152,89	18,67
HDL	56,25	1,78
LDL	102,88	13,48
Triglycerides	118,13	41,20
Phosphatase alkaline	105,30	17,84

general, these symptoms are controlled with analgesic medication.³ Myalgias occur in 15% of the cases, based on data from the literature.¹⁸ This is compatible with the results obtained in this work. Muscle alterations with increased CPK levels have been reported in 16 to 51% of the patients with acne treated with isotretinoin.¹¹ In 2001, Landau et al. published a study in which they evaluated the incidence, course, and clinical significance of increased CPK levels in patients with acne treated with isotretinoin. Of the 442 patients evaluated, seven had CPK levels above 5,000UI/l; of these, only two complained of myalgia. Physical activity or intramuscular injection before the blood test were reported by six patients, and CPK levels returned to normal after the end of treatment. The authors concluded that increased CPK levels with or without myalgia during treatment with isotretinoin is a benign phenomenon.¹¹ CPK levels were not measured in our patients and they were advised to avoid intense physical activities and to use analgesic medication with control of the clinical condition. There is a report in the literature of atrial tachycardia (confirmed via Holter monitoring for 24 hours) secondary to the use of isotretinoin in a male patient, 16 years old, one week after the start of treatment. After the drug was discontinued, symptoms disappeared.²⁵ The time relationship between the use of the medication and the development of symptoms led the authors to suggest a causal relationship with the drug. We should pay attention to this possible rare effect of isotretinoin. It was not possible to collect more investigative data about this patient because it was a retrospective study. There were no reports of psychiatric complaints by our patients. This is a fact that causes concern to many physicians when prescribing isotretinoin. As previously mentioned, there are still questions about the association of the drug with depression or suicide.^{13,14} A cohort study conducted in Canada compared the relative estimated risk of suicide among patients with acne treated with isotretinoin or oral antibiotics. The study included 7,535 patients being treated with isotretinoin and

14,376 patients being treated with oral antibiotics. An association between the use of isotretinoin and an increased risk of suicide was not found.¹⁴

The analysis of laboratory exams showed a discreet, nearly insignificant, variation of hepatic enzymes. In the same way, cholesterol levels and their fractions and alkaline phosphatase levels varied very little (Table 1, Graph 3). Triglyceride levels, on their turn, varied to a greater extent, in accordance with data from the literature.²¹ None of these alterations were statistically significant. The medication did not have to be suspended and there was no need to adjust the dose to the patients' needs.

The patients studied showed adverse effects compatible to those found in the literature researched. These effects were mostly controlled with symptomatic medication and there was no need to suspend the drug in any of the cases. Systemic effects were rare. Because our study had a retrospective design, it was difficult to evaluate in greater detail the patient that presented tachycardia and confirm if the effect was secondary to the use of isotretinoin. However, it serves to alert about the possible occurrence of this dangerous effect.

Most of our patients had had level 3 or 4 acne for a long time. For this reason, the improvement of their condition with the use of the drug overrode the discomfort of the side effects. Despite the drug being safe and tolerable, a routine clinical and laboratory evaluation and a good doctor-patient relationship are extremely important for the success of the treatment.

CONCLUSION

Based on the data analyzed and what has been described in the literature, isotretinoin is a safe drug with well-tolerated laboratory side effects.

The excellent results obtained with the use of isotretinoin by patients with moderate to severe acne override the hematologic and biochemical alterations that they may suffer.

It is crucial to emphasize the teratogenic effects of isotretinoin and the use of a contraceptive method to female patients being treated with the drug.

Isotretinoin is a drug that can be safely used with adequate monitoring to treat cases of acne vulgaris when the benefits outweigh the risks. □

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MAILING ADDRESS / ENDEREÇO PARA CORRESPONDÊNCIA:
Maria de Fátima de Medeiros Brito
Av. Beira Rio, 290/1601 - Ed. Saint Gabriel
50750 400 Ilha do Retiro - Recife - PE, Brazil
Phone: 81 3226 6994 - 81 8887 7168
Email: fatimabrito2@gmail.com

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