Adult women with acne have a higher risk of elevated triglyceride levels with the use of oral isotretinoin

Mulheres adultas com acne apresentam maior risco de elevação de triglicerídeos ao uso de isotretinoína oral

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Abstract: There are restrictions associated with the use of isotretinoin because of its effects on the lipid profile. The records of ninety patients treated with this medication were reviewed to identify factors that would predispose patients to these abnormalities. A significant increase in cholesterol and triglyceride levels occurred. Patients in whom triglyceride levels increased were more likely to be female, although this difference was not present at baseline. Women with persistent acne may constitute a risk population for these side effects.
Keywords: Acne vulgaris; Hyperlipidemias; Isotretinoin; Retinoids; Women

Resumo: A isotretinoína apresenta restrições relacionadas a efeitos no perfil lipídico. Revisaram-se 90 pacientes tratados, em busca de fatores predisponentes a essas alterações. Houve elevação significativa do colesterol e triglicerídeos. Os pacientes em que estes últimos mostraram essa alteração foram, em sua maioria, do sexo feminino, predileção que não ocorria com as alterações iniciais. Mulheres com acne persistente talvez representem população de risco para tais efeitos colaterais.
Palavras-chave: Acne vulgar; Hiperlipidemias; Isotretinoína; Mulheres; Retinoides

Acne is one of the principal complaints in dermatology clinics and although it is self-limiting in the majority of cases, the condition has a significant psychosocial effect on the patient and may leave permanent unsightly scars. [1] Oral isotretinoin is known to be the only medication able to inhibit this pathology; however, its use involves restrictions principally related to its effects on the liver, changes in the lipid profile and its teratogenicity. [2,3] In routine clinical practice, although discontinuation of the medication due to an increase in triglycerides (TG) is rarely necessary, elevated TG levels constitute a concern, leading to a reduction in the doses used until laboratory tests return to normal. With this in mind, a brief review was made of the medical charts of patients treated in this institution with the objective of identifying factors indicative of a predisposition to alterations in serum lipids with the use of oral isotretinoin.

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Data from the medical records of patients to whom oral isotretinoin had been prescribed for the treatment of acne between 2005 and 2009 at the Pró-Hansen Foundation in Curitiba, Paraná, Brazil were retrospectively reviewed. Data evaluated consisted of: age at the beginning of use of the drug, duration of the condition of acne, gender, weight, dose used at the time serum lipid tests were conducted, the presence of other pathologies, the use of other medication, the clinical grade of acne at the time oral isotretinoin was prescribed, serum total cholesterol (TC) and TG levels prior to use of the medication and the highest levels registered on the medical charts for the respective lipids for up to nine months after initiation of the medication. TG levels > 150 mg/dl and TC levels > 200 mg/dl were considered abnormal. Fisher's exact test, the chi-square test, Student's t-test and the Mann-Whitney-Wilcoxon test were used in the bivariate analyses depending on the sample size and the non-normality of distribution according to the Lilliefors test ($p<0.05$). Analysis of covariance (ANCOVA) was performed, with the highest TG levels registered during treatment as the dependent variable and considering only those patients for whom no data were missing for any of the variables included in the model: gender, age, daily dose of oral isotretinoin according to weight and previous TG levels.

A total of 90 treatments were included, with 5 cases of retreatment (6%). The median age of patients was 19 years, the majority were male (66%) and the median duration of the disease was 4 years. The median dose of the medication per weight was 0.60 mg/kg/day and was significantly higher for the women compared to the men. The most common clinical grade was grade III, with grade IV being more common in the men, while grade II was more common in the women. Likewise, the women tended to be older at the beginning of treatment (Table 1).

TC and TG levels changed significantly from baseline levels during use of the medication. Mean TC levels increased from 152 ± 32 mg/dl prior to treatment to 174 ± 39 mg/dl following the initiation of

Table1: Clinical and laboratory characteristics according to gender

Variable	Total n=90	Females 31 (34%)	Males 59 (66%)	Odds Ratio (95%CI)	p-value
Clinical characteristics at the time treatment was prescribed					
Age (years) [a]	19 (5.75)	22 (7)	18 (3)	-	<0.01
Duration (years) [a]	4 (3.5)	5,25 (4)	3,5 (2.5)	-	0,12
Grade II[b]	24 (27%)	14 (45%)	10 (17%)	4.04 (1.51 – 10.77)	<0.01
Grade III[b]	49 (54%)	16 (52%)	33 (56%)	0.84 (0.35 – 2.01)	0,7
Grade IV[c]	17 (19%)	1 (3%)	16 (27%)	0.09 (0.01 – 0.71)	<0.01
Other drugs used [c]	25 (28%)	22 (71%)	3 (5%)	45.63 (11.29 – 184.42)	<0.01
Re-treatment[c]	5 (6%)	1 (3%)	4 (7%)	0.46 (0.05 – 4.29)	0.66
Weight (kg)[d]	66 (12.2)	60 (11,5)	69 (11.7)	-	<0,01
Dose (mg/kg/day)[a]	0.6 (2.2)	0.63 (0,12)	0.56 (0.19)	-	0.03
Proportion of abnormal tests at baseline					
Cholesterol[c]	7 (8%)	2 (7%)	5 (9%)	0,76 (0.14 – 4.16)	0.99
Triglycerides[c]	6 (8%)	2 (7%)	4 (8%)	0,90 (0.15 – 5.27)	0.99
Proportion of abnormal tests during treatment					
Cholesterol[c]	12 (18%)	8 (32%)	4 (10%)	4,32 (1.15 – 16.47)	0.04
Triglycerides[c]	18 (27%)	12 (48%)	6 (15%)	5,38 (1.67 – 17.33)	<0.01
Proportion of abnormal tests during treatment for patients >17 years of age (n=42)					
Cholesterol[c]	9 (21%)	6 (32%)	3 (13%)	3,08 (0.65 – 14.52)	0.26
Triglycerides[c]	15 (38%)	11 (58%)	4 (19%)	5,84 (1.41 – 24.17)	0.02

[a] Mann-Whitney-Wilcoxon test (median and interquartile difference); [b] Chi-square test; [c] Fisher's exact test; [d] Student's t-test (mean and standard deviation).

treatment (mean ± standard deviation), $p<0.01$; Student's t-test. Median TG levels increased from 72 mg/dl to 102 mg/dl (interquartile difference: 42 and 92, respectively), $p<0.01$; Mann-Whitney-Wilcoxon test. Of the patients with normal TG levels at baseline, changes occurred in 28% of cases. Of the patients with normal TC levels at baseline, 13% went on to present alterations.

Patients who developed alterations in TG and TC levels during treatment were more likely to be female; however, this difference was not present prior to the use of oral isotretinoin. The difference between genders with respect to the rate of altered TG levels during treatment remained when analysis was restricted to patients over 17 years of age; however, there was no statistically significant difference in the subgroup of patients under 17 years of age (Table 1). In the multivariate analysis by ANCOVA, a positive correlation was found between the maximum TG levels recorded during treatment and baseline values ($p<0.01$) and being female (coefficient = 32.37; $p = 0.04$). The latter association appeared to gain strength when analysis was restricted to patients over 17 years of age (coefficient = 49.51; $p = 0.02$).

These data are in agreement with previous observations on the effects of oral isotretinoin on serum lipids, indicating that baseline levels are the greatest determinants of levels reached during treatment; however, these findings also suggest that increases are higher in women with acne. [2,4] The women in this sample developed the condition later, possibly representing cases of female adult acne in part of these cases. Women with persistent acne may constitute a population that is more susceptible to these effects of oral isotretinoin. Retinoid X receptors (RXR) are known to play a role in the control of cell metabolism and have already been implicated in the metabolic syndrome and in triggering polycystic ovary syndrome. [5,6] Rodondi et al. identified a propensity to develop the metabolic syndrome in patients who had a pronounced elevation in TG levels during use of oral isotretinoin, suggesting the participation of genetic factors. [7] These correlations may help explain the apparent propensity of women to develop high TG levels, as found in the present study, particularly in adult women with persistent acne. Possible inconsistencies in data that are inherent to retrospective studies may have affected the present findings. Furthermore, this study was unable to evaluate the role of hormonal contraceptives, often used together with oral isotretinoin, in the abnormal laboratory findings. Nevertheless, further studies with more robust design should be conducted to investigate the observations presented in this report. ❑

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