# Changes in Laboratory Variables Induced by Isotretinoin Treatment of Acne

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During a trial of isotretinoin (0.5 mg/kg body weight/day for 3 months) in 90 patients with severe acne, the leucocyte (WBC) count, and particularly the number of neutrophils, decreased significantly. In patients with a good response the mean WBC count fell by 24% and the neutrophils by 33%, whereas in those with a poor response these variables decreased by 8% and 14%, respectively. The serum ALAT, ASAT, cholesterol and triglyceride levels increased significantly. Patients with a poor response ($n$=35) received a higher dosage (0.75 mg/kg) for an additional 3 months, and during this period there was a further decrease in the WBC and neutrophil counts and an increase in the triglyceride level. In the other patients, who initially responded well, the dosage was decreased to 0.1 or 0 mg/kg during the second 3-month period, which resulted in reversion of the laboratory variables to the pre-treatment levels. The observed changes were clearly both dose-dependent and reversible. *Key words: Leucocytes; Neutrophils; Transaminases; Cholesterol; Triglycerides.* (Received June 3, 1985.)

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The clinical efficacy of oral isotretinoin (13-cis retinoic acid, Roaccutane®) in the treatment of severe acne is now well established; so are the clinical side effects of the drug. On the other hand, the influence of the drug on different laboratory variables has only been described in a few reports. During a trial of isotretinoin we observed some changes in laboratory values which had either not been reported previously or had not been observed at the dosages used in this study.

## METHODS

The trial comprised 90 patients (73 men and 17 women) of ages 16–30 years with severe nodulocystic acne. Other forms of treatment for acne had been discontinued one month before entry into the trial. The women were either taking oral contraceptives or using intrauterine devices. The study was approved by the Ethical Committees of the Medical Faculties in Uppsala, Stockholm and Göteborg. The design of the study is shown in Fig. 1. As seen in the figure, all patients received the same dosage of isotretinoin (0.5 mg/kg b.w./day) during the first 3 months of the trial. During the following 3-month period those who showed a good response (≥2/3 improvement) were randomly allocated to groups receiving either no treatment (=0 mg group) or 0.1 mg/kg of isotretinoin. Those who did not respond satisfactorily were given isotretinoin 0.75 mg/kg during the second 3-month period.

The following measurements were made before and after 1, 3, 4 and 6 months of treatment: haemoglobin; total and differential leucocyte counts; platelet counts; serum creatinine, bilirubin, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), alkaline phosphatase, cholesterol and triglycerides. These variables were all measured as part of routine laboratory analyses. The patients were fasting when the blood samples were drawn in the morning.

For statistical evaluation the paired $t$-test was used.

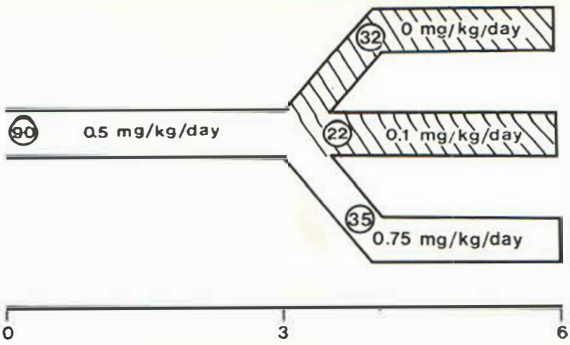


*Fig. 1.* Design of the trial.

## RESULTS

The overall clinical effects of the treatment were good and are reported elsewhere (1).

The values for laboratory variables that were significantly altered after 3 months of treatment are given in Table I. Notable changes during the second 3-month-period are depicted in Fig. 2. The different variables are discussed separately below.

### *Haematological parameters*

*Haemoglobin.* The concentration decreased significantly during the first 3 months. During the second period (3–6 months) the patients whose treatment had been discontinued showed significant increase in haemoglobin concentration, whereas in those in the group receiving 0.75 mg/kg the concentration remained depressed (data not shown). Isotretinoin-induced changes in the haemoglobin concentration has not been reported previously and the biological relevance is not clear.

*White blood cells (WBC).* In the group as a whole the total WBC count decreased by an average of 17% and the neutrophil count by 24% during the first 3 months. In patients with a poor response these decreases were 8% and 14%, respectively, as compared with 24% and 33% in those with a good response.

During the second 3-month period, when the poor responders were treated with 0.75 mg/kg of isotretinoin, these patients exhibited a further decrease in WBC and particularly of the neutrophils (Fig. 2, upper panel). After 6 months of treatment the mean WBC count

Table I. *Laboratory variables (mean ± SEM) which changed significantly during the first 3 months of the trial with isotretinoin (0.5 mg/kg; n=89)*

| | Before | After 3 months | Degree of stat. sign. |
|---|---|---|---|
| Haemoglobin, g/l | 149±1.3 | 146±1.3 | $p<0.01$ |
| Leucocytes, $\times 10^9$ cells/l | 8.0±0.2 | 6.7±0.2 | $p<0.01$ |
| Neutrophils, $\times 10^9$ cells/l | 5.4±0.2 | 4.1±0.2 | $p<0.01$ |
| S-ALAT, μkat/l | 0.30±0.02 | 0.38±0.03 | $p<0.05$ |
| S-ASAT, μkat/l | 0.34±0.01 | 0.44±0.02 | $p<0.01$ |
| S-Cholesterol, mmol/l | 4.56±0.10 | 4.97±0.12 | $p<0.01$ |
| S-Triglyceride, mmol/l | 1.06±0.08 | 1.27±0.06 | $p<0.05$ |
| S-Creatinine, μmol/l | 83.8±1.6 | 80.3±1.7 | $p<0.05$ |

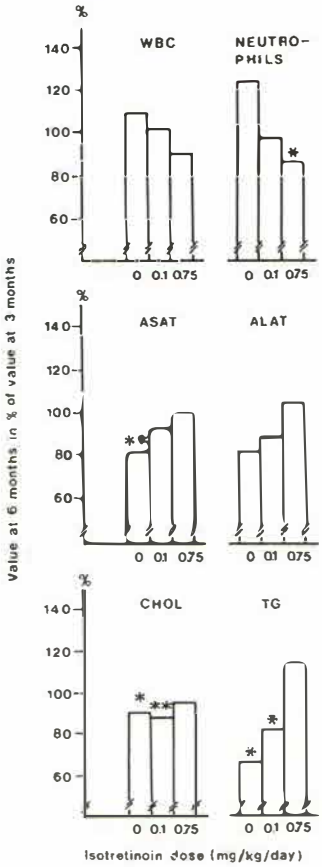


*Fig. 2.* Dose-related changes in some laboratory variables during the second 3-month period of the trial. *Denotes statistical significance of difference compared with the 3-month value at the 5% level; **at the 1% level. CHOL = cholesterol; TG = triglycerides.

in this group had fallen from an initial value of 8.2 to $6.9\times10^9$ cells/l (−16%) and the mean number of neutrophils from 5.5 to $3.9\times10^9$ cells/l (−29%).

*ASAT and ALAT*

During the first 3 months there was a significant increase in the ASAT and ALAT values. The changes in the second period are illustrated in Fig. 2, middle panel. The values were largely unchanged in those taking 0.75 mg/kg whereas in the other patients they returned to near pre-treatment levels. Clearly abnormal values were rare and only one ASAT and two ALAT values were above the upper normal limit during the trial.

*Cholesterol and triglycerides*

Both these variables increased during the first 3 months. Fig. 2 lower panel illustrates the changes during the second period. The mean serum cholesterol decreased significantly in the patients receiving 0 and 0.1 mg/kg isotretinoin, whereas in the 0.75 mg/kg group the mean value remained elevated.

There was also a significant decrease in the mean triglyceride values in the 0 and 0.1 mg groups. On the other hand, the group receiving 0.75 mg/kg showed a further increase and after 6 months the mean value was 52% above the pre-treatment value. Seventeen patients had serum triglyceride values above the upper normal limit on one or several occasions during the treatment and one patient had to discontinue the treatment because of a high triglyceride value.

*Other laboratory variables*

No marked changes were observed in the numbers of eosinophils, basophils, monocytes or thrombocytes, or in the serum bilirubin concentration. A slight but significant decrease in the serum creatinine value was observed during the first 3 months, but there was no significant change in the second period.

No significant change in the mean alkaline phosphatase value was observed during the first 3 months, but during the second period it decreased significantly in both the 0 and the 0.1 mg/kg group. In the patients receiving 0.75 mg/kg the mean value was the same at 3 and 6 months.

## COMMENTS

In this study an initial dosage of isotretinoin of 0.5 mg/kg body weight per day for 3 months resulted in a good clinical response in 60% of the patients (1). In spite of the moderate dose, significant changes in several of the laboratory variables occurred. The design of the trial with three different dosages in the second period yielded some information about the dose-dependency of the changes.

The most marked change was noted in the number of leucocytes, particularly the decrease in neutrophils. In the first period the neutrophils fell by 33% in patients who responded well to therapy, whereas the reduction was only 14% in those with an unsatisfactory response. When the latter group was given a higher dosage, resulting in a better clinical response, their WBC and neutrophil counts decreased in the same way as in those who had responded satisfactorily in the first period of the trial. A significant reduction in the WBC count after isotretinoin treatment (0.5–1.0 mg/kg) was recently reported by van der Meeren et al. (2). They gave no data for neutrophils and no information about the relation between the clinical response and the decrease in the number of neutrophils. Although a reduction in WBC may be secondary to reduced disease activity, it may also indicate a mode of action of isotretinoin, namely that it suppresses the neutrophils. There are infact reports on the influence of isotretinoin on neutrophil activity (3, 4, 5) that may suggest that an inflammatory process may be modulated by this compound.

Although the transaminases (ASAT and ALAT) were mostly within normal limits during the study period there was a tendency towards elevated values, possibly indicating a slight hepatotoxic effect. Influence of isotretinoin on liver function tests has also been reported by Marsden et al. (6). With a dosage of 1 mg/kg they found increasing $\gamma$-glutamyl transpeptidase levels and also increased ASAT and alkaline phosphatase levels. However, the adverse effects on liver function tests appear to be reversible.

It is known that isotretinoin, at least in a dosage of 0.6 mg/kg, induces an increase in the serum levels of triglycerides and cholesterol (7). These effects were further illustrated in the present study, and, especially that on triglycerides, were clearly dose-dependent.

In women it is possible that the concurrent use of oral contraceptives may enhance the tendency to hyperlipidaemia during isotretinoin treatment. However, few women (5/35) were in the 0.75 mg/kg group and therefore it seems unlikely that the pronounced lipid elevations in this group were to any noticeable degree attributed to oral contraceptives.

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