

LONG-TERM EFFECTS AFTER TOPICAL APPLICATION OF ACTIVE RETINYL PALMITATE.

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Synopsis

A randomised double-blind within subject study comparing two galenical formulations of retinyl palmitate (RP), a conjugated and an unconjugated one, showed significant differences in favour of the conjugated formulation with respect to improvement in objective and subjective skin parameters on the volar part of the forearms. The treatment period was 3 months, and 20 female subjects took part in the study. In order to study the duration of the effect, objective measurement of skin elasticity and thickness as well as subjective evaluations by the subjects, were repeated 12 months after cessation of treatment. The results of the study show, as can be expected, that improvements in skin parameters will vanish over time. However, after treatment with the active formulation, still about 25% of the improvements in the objective skin parameters obtained after a treatment period of 3 months are detectable after a 12 month treatment-free period. These results indicate that less frequent administrations of active RP can be used during maintenance treatment.

Riassunto

Con uno studio randomizzato a doppio cieco sono state controllate differenti formulazioni galeniche di retinolo palmitato (RP) in forma libera e coniugata.

I risultati ottenuti hanno dimostrato differenze significative a vantaggio della forma coniugata con le diverse metodiche utilizzate sia soggettive che obiettive. Il periodo di trattamento si è protratto per tre mesi con un gruppo composto da 20 volontari di sesso femminile.

Per valutare la durata dell'effetto dodici mesi dopo l'interruzione del trattamento è stata verificata sia l'elasticità e lo spessore della cute mediante l'utilizzo di metodiche obiettive che l'aspetto generale della pelle mediante valutazioni soggettive. Come si prevedeva la maggior parte dei miglioramenti ottenuti sui diversi parametri cutanei si vanifica con il trascorrere del tempo.

Comunque, dopo trattamento con la formula attiva il 25% circa dei miglioramenti ottenuti permangono anche dopo 12 mesi dall'interruzione.

Questi risultati indicano che possono essere utilizzate applicazioni meno frequenti dell'attivo RP durante il periodo di mantenimento.

Introduction

Treatment of the human skin with water solubilized retinyl palmitate (RP) ointment for a period of 3 months with bid administrations induces significant changes in skin thickness and skin elasticity as well as visual changes evaluated by the users. We have recently published a study showing the abovementioned effects (1). The essential prerequisite for obtaining clinical effect following topical administration with RP is that the formulation is in an active form, meaning that the skin penetration is satisfactory (2,3). Only in this way can the necessary transformation of the ester (RP) into retinoic acid (RA) in the skin take place and the biological effect of RA be exerted.

By using the active RP, a pro-drug principle is utilized applying a biological inactive substance which in turn is metabolized to the active form in the skin. Treatment with different concentrations of RA has in several well performed studies been shown to have significant effects on the aging symptoms of the skin, especially on the photoaging changes (4,5,6). However, a main problem with the use of RA can be the side-effects of the dermatitis type after prolonged use. The skin tolerability for RP, on the other side, is excellent and therefore, in the active form, well suited for daily use as a *cosmoceutic* in the treatment of aging symptoms.

The visual and measurable effects on the skin require a treatment period of at least 3 months, using the agent twice daily. Questions have been raised if and to what extent the therapeutic effect will be reduced if treatment is stopped, or whether it is required with a life-long treatment with optimal doses, or if a maintenance dose can be used when the effect of RP once is established.

To our knowledge relatively little information have been published on the long-term effect of antiaging treatment, the possible reversibility of the symptoms following cessation of therapy, and to what degree maintenance therapy is sufficient (4,5,6).

On this background we decided to carry out a study to investigate the long-term effect of RP-treatment in a group of subjects having been treated for a period of three months.

Material and methods

The aim of the study was to investigate if and to what extent a short-time treatment (3 months) with RP had long-term effects on skin parameters such as skin thickness, skin elasticity and visual skin quality.

The present study is a long-term follow-up of our previous short-term study. The 20 female subjects taking part in the short-term study were invited to participate.

After concluding the comparative double-blind study using either conjugated (Formulation A) or none-conjugated (Formulation B) RP on the volar part of the forearms for a period of three months, none of the subjects had used topical and/or systemic treatment for aging symptoms.

After a therapy-free period of exactly 12 months, the participants were invited to remeasurements of skin thickness and skin elasticity with the same method as used in the short-term study. The instrument used are the DERMA-SCAN A and the DERMAFLEX (Cortex Ltd., Århus; Denmark), which in several well-performed studies have been validated to give reliable results for these two parameters (7). In addition the subjects were asked to judge the difference in visual skin quality (smoothness and glow), between the two previously treated forearms by giving preference to the arm they thought had the best skin quality. The choices were right or left arm respectively or no difference between the arms.

A separate study to objectify and check the blindness of the initial double-blind study was also carried out. Each of the earlier treated women were asked once again to test the two different formulations; the conjugated (Formulation A) and the unconjugated (Formulation B) form of RP, and were asked to rate the ointments accor-

ding to the cosmetic properties. The answering alternatives were preference for formulation A or B or no difference between the formulations.

Results

Study population

All the 20 female subjects participating in the short-term study responded positively and took part in the follow-up study. The mean age was 51.3 years (SD 6.4).

Efficacy parameters, skin thickness and elasticity

All skin parameters were measured by the same person (ET), who also performed the measurements in the short-term study. Measurements were performed at the mid-region of the volar part of the forearms. All measurements were done in triplicate and the average values were used for statistical evaluation.

The results from the DERMASCAN and the DERMAFLEX measurements are shown in Tables I and II, respectively.

As can be seen from Table I, the skin thickness

is reduced from the average value of 1.19 mm after therapy to 0.98 mm after 12 months of no treatment. During the short-time study the skin thickness on the arm treated with the active ointment increased from the average value of 0.91 mm to 1.19 mm, e.g. an increase of about 31%. During the therapy-free period the skin thickness is reduced to an average value of 0.98 mm meaning that about 75% of the therapy effect is lost. By other words about 25% of the original therapy effect as regards skin thickness is still present after a therapy-free period of one year.

Comparing the arms treated with conjugated (A) and the none-conjugated (B) ointments the difference in skin thickness is 0.09 mm after one year, which is a significant difference ($p < 0.05$). As can be seen from Table II, the skin elasticity is reduced from the average value of 71.5% after therapy to 63.0% after 12 months of no treatment. During the short-time study the skin elasticity on the arm treated with the active ointment increased from the average value of 60.4% to 71.5%, e.g. an increase of about 18%. In the therapy-free period the skin elasticity is reduced to 63.0%, meaning that 76.6% of the therapy effect as regards skin elasticity is lost. By other words about 23.4% of the original therapy effect is still present after a therapy-free

Table I

Changes in skin thickness (mm) during a 12 month period after cessation of therapy with RP ointments compared with values at the end of a 3 month treatment period.

Arm treated with formulation		End of short-term study	After 12 months
A*	Mean (SD)	1.19 (0.10)	0.98 (0.09)
	Range	0.87 - 1.32	0.75 - 1.25
B	Mean (SD)	0.93 (0.10)	0.89 (0.10)
	Range	0.74 - 1.10	0.71 - 1.10

Table II

Changes in skin elasticity (%) during a 12 month period after cessation of therapy with RP ointments compared with values at the end of a 3 month treatment period.

Arm treated with formulation		End of short-term study	After 12 months
A*	Mean (SD)	71.5 (7.9)	63.0 (7.3)
	Range	50.9 - 84.2	45.9 - 80.2
B	Mean (SD)	60.2 (6.5)	59.2 (7.0)
	Range	44.7 - 70.4	44.0 - 70.1

period of one year. Comparing the arms treated with conjugated (A) and none-conjugated (B) ointments the difference in skin elasticity is 3.8% after one year which is statistically significant ($p < 0.05$).

Discussion

The result from the present study shows that some of the significant changes obtained by a 3 month treatment with an active (conjugated) RP ointment, in skin thickness, skin elasticity and visual skin quality are still detectable one year after cessation of therapy. Approximately 25% of the original effect in the objective parameters following treatment with active RP is still present after one year.

To our knowledge no clear-cut recommendations have been given how long-term antiaging therapy with topical agents, that either be RA or RP, should be given. In one study no change in skin parameters could be detected after a one month cessation of treatment with RA (4), while in another study a maintenance treatment with administration of RA 3 to 4 times a week (6), as compared to daily administrations during the active treatment phase, is recommended. The data backing these recommendations are, however, limited. For the long-term use of RP we have not been able to find dose recommendations

at all. The data from our study do, however, indicate that the effect of RP-treatment will vanish if the treatment is stopped even if a not negligible part of the effect is still present after a treatment-free period of 12 months.

Several factors have taken into consideration when recommending maintenance treatment with RP for aging symptoms of the skin. At present we have no knowledge of how long time treatment should be given before maximum effect is established. From the literature it seems that treatment periods of 8-12 months, or even longer, with RA will be necessary in order to obtain maximum effect. A similar (or longer) treatment will probably also be needed for RP.

After obtaining the effect of RP during a three months treatments, we anticipate from these data that further studies could be performed showing the optimum treatment time for reaching the maximum effect on skin thickness and elasticity. We suggest already now that an application once daily may be sufficient to maintain the results of the earlier reached effect of RP.

Visual difference in skin quality.

The subjects preference for skin quality on the arms are listed in Table III, and are related to

Table III
Subject preference (N=20).

	Arm treated with		No difference
	A*	B	
Best skin quality	11	3	6

Table IV

The distribution of subjects giving preference to the two ointments (N=20).

	No. of subjects
A*	8
B	7
No difference	5

the treatment schemes. The subjects were giving preference without knowing the treatment randomization in the short-term study.

As can be seen from the table, it is a significant preference for the arm that had been treated with the active RP-ointment during the short-term study ($p < 0.05$).

Objectifying the blindness of initial study

In order to test if the blindness of the original study was really valid, the participants were asked to judge the ointments from a cosmetic point of view. The results are presented in Table IV. As can be seen from the Table IV, no difference in preference was detectable and thus it was probably not possible to identify the active form of the ointment during the double-blind part of the study.

* Trade Name: Sincera®, Medicina AB, Lund.

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