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# Randomised, placebo-controlled, double-blind, split-face study on the clinical efficacy of Tricutan® on skin firmness

B. Sommerfeld*

*Dermatology Clinic, Danavägen 7B, SE-18131 Lidingö, Sweden*

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## Abstract

Tricutan is a combination product of herbal extracts traditionally used for treatment of skin conditions, together with dimethylaminoethanol. The effectiveness of Tricutan in improving skin firmness and elasticity in photoaged facial skin was examined in a randomised, placebo-controlled, double-blind, split-face study in 28 women, 34–67 years old. Treatment with Tricutan and placebo was given for 4 weeks. Skin firmness and elasticity was evaluated using the speed of propagation of ultrasound shear waves in the skin as end point (Reviscometer RVM 600).

The study was completed by 25 women. The Tricutan treatment resulted in a significantly reduced propagation speed indicating increased firmness. There was no immediate effect by Tricutan application on propagation speed. At self evaluation the women evaluated the treatment effect of Tricutan to be significantly better than the treatment effect of placebo. The clinical evaluation also showed Tricutan to give a significantly better treatment result than placebo. Tolerance to Tricutan was generally good. However, three women did not complete the study because of mild irritative contact dermatitis.

The results show that Tricutan can increase skin firmness both objectively and subjectively. Further studies are warranted, especially to investigate if Tricutan can delay the need for surgical face-lift procedures.


***Keywords:*** Skin firmness; Photoaging; Cosmeceutical; Herbal extract; Double-blind study

## Introduction

Skin appearance is only moderately affected from childhood to old age on the parts of the body that are not exposed to sunlight. Clinically, chronological ageing causes a thinner and less elastic skin compared to the skin in childhood. Contrary, skin areas exposed to sunlight show characteristic clinical changes in the elderly. UV radiation is the main factor speeding the ageing process in the skin. The bronzed young faces of today will become the wrinkled prune-like ones of tomorrow. Wrinkles are a major consequence of photoageing of the skin. Pigment changes like hypopigmentation, hyperpigmentation, seborrhoeic warts, dry skin, "broken veins"-teleangiectasia, "boomerangs scars" are some more changes associated with sun damage. UV radiation has an immunosuppressive effect, and may lead to DNA changes and skin carcinoma.

Areas most affected, such as hands and face, are also those most visible in our social life. Although facelifts can smooth wrinkles out, there is no way to reverse this skin damage by UV radiation fully. The last 10 years we have observed an increase of consumers' demand of

*Tel./fax: +46 87677288.
*E-mail address:* bea.hudmott@telia.com.

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non-invasive procedures and looking younger without surgery has become a trend.

Topical therapies against the symptoms of skin photoageing have been tried with varying success. Retinoids have been shown to be useful to some patients (Sorg et al., 2005, 2006; Stratigos and Katsambas, 2005). Topical antioxidants may be shown to be a promising mode of treatment (Burke, 2004). A variety of other agents have been tried including various herbal extracts (Rona et al., 2004). Recently Tricutan®, a new combination of herbal extracts traditionally used in China and India and the Mediterranean area together with the choline analogue dimethylaminoethanol (DMAE), has been introduced for the treatment of the symptoms of photoageing in skin. The components of Tricutan, extracts of Rosmarinus officinalis (rosemary), Centella asiatica (gotu kola), tetrahydrocurcumin derived from Curcuma longa (tumeric), and DMAE, have all been shown to have beneficial effects on skin (Calabrese et al., 2001; MacKey and Miller, 2003; Grossman, 2005; Panchatcharam et al., 2006).

The active components of the Tricutan gel are Rosmarinus officinalis (rosemary), water extract, 0.3%, Centella asiatica (gotu kola), butylene glycol extract, 1.0%, tetrahydrocurcumin dry extract derived from Curcuma longa (tumeric), 0.1%, and DMAE, 3%. The excipients in Tricutan are well known ingredients used to form the gel. The combined action of the active components of Tricutan could be expected to have a beneficial effect on firmness in photoaged skin.

In the present study the influence of Tricutan on skin firmness and elasticity as well as on subjectively perceived improvement of skin appearance has been evaluated in a randomised, placebo-controlled, double-blind, split-face study. Also the acute effect of administration of Tricutan was examined, as a pilot experiment had suggested that skin firmness could be affected already within 45 min after application (AddermaAB, Stockholm, Sweden, data on file).

## Patients and methods

The study was a randomised, double-blind, placebo-controlled, single-centre, split-face outpatient study with treatment for 4 weeks. The study was approved by the local ethical committee and was conducted according to Good Clinical Practice. All included volunteers gave their signed informed consent before entering the study.

Twenty-eight women between 34 and 67 years in good physical and psychical condition with Fitzpatrick skin types I, II or III responded to advertisements in local daily newspapers regarding the opportunity to participate in the present clinical study, and were found to be eligible for inclusion. Exclusion criteria were pregnancy or nursing, known allergy to any of the components in Tricutan, any abuse of drugs or ethanol, any skin disease in the face, use of any topical or systemic skin treatment later than 1 month before the start of the study, any peeling, laser treatment, skin scraping or other skin surgical measures in the face later than 1 year before the start of the study.

The investigation started with an initial clinical examination to check the eligibility to the study according to the inclusion and exclusion criteria. The baseline investigation of facial skin firmness was conducted. The skin appearance was evaluated clinically and by the patient according to questionnaires for different evaluation variables, one questionnaire for the woman and another one for the doctor. Two coded 30 g bottles, marked "right" and "left", respectively, for use twice daily, mornings and evenings, during the 4-week treatment period were distributed. One of the bottles contained Tricutan gel (Dermyn™), the other bottle contained placebo gel without Tricutan. The gels used for the study were provided by Adderma AB, Stockholm, Sweden. Tricutan is a patent pending complex of substances for treatment of photoaged facial skin. Tricutan contains a defined extract of Rosmarinus officinalis (rosemary) with a high concentration of ursolic acid encapsulated in liposomes, a defined extract of Centella asiatica (gotu kola), tetrahydrocurcumin derived from Curcuma longa (tumeric), and dimethylaminoethanol, an analogue of choline. The placebo gel was identical in smell, colour and consistency to the Tricutan gel. A coded list was used to determine if the right or the left side of the face should be treated with the active product or the vehicle. Each participating woman received a bottle of a mild soap and a bottle of moisturising cream in order to standardise conditions that could affect the facial skin. The women were advised to continue their daily routines concerning make up.

Skin firmness, the primary efficacy variable, was assessed at the start of the trial and after treatment for 28 days using a devise to measure shear wave propagation in the skin, Reviscometer RVM 600® (Courage + Khazaka Electronic, Cologne, Germany), for recording Resonance Running Time, RRTM, expressed in arbitrary time units. Skin firmness was assessed by measuring the speed of transmission of a 500-MHz mechanical signal through the skin. A lower value for the RRTM is indicative of a firmer, more elastic skin (Uhoda et al., 2002; Uhoda and Pierard, 2003; Dang et al., 2005).

The first set of measurements of baseline skin firmness on the right and on the left part of the face was made at the start of the study, just before the first topical application of the treatment gels on the right and on the left part of the face. The second set of measurements of skin firmness on the right and on the left part of the face was made after treatment with the study gels for 4 weeks. A third set of measurements of skin firmness on

the right and on the left part of the face was made 15 min after application of the treatment gels in the patients that had been treated for 4 weeks. This third set of measurement was made to investigate if an effect could be registered as early as 15 min after application of the gels. Measurements were made on both cheeks at a fixed position of the probe. RRTM values were recorded in four directions (0°, 90°, 180°, 270°) with the average value being used as assessment of general skin firmness. The difference between the active and the vehicle side of the face was analysed statistically using the Wilcoxon matched pairs rank test.

A self-assessment form was filled in by each participating woman on two occasions, at the start of treatment and after 4 weeks of treatment, and was handed over to the study nurse before the clinical evaluation. Two clinical evaluations were made by the same dermatologist at the start of the treatment and after treatment for 4 weeks. A clinical protocol with evaluation of left and of the right side of the face was filled in. Estimate of treatment effect on each side of the face was graded from 0 to 6 with 0 = worsening of skin appearance, 2 = no change, and 6 = excellent improvement. The statistical power analysis was based on an estimate of the proportion of women showing improvement on the side of the face treated with Tricutan. Using a $\chi^2$-test for proportions in a group of 28 subjects a power of 80% is achieved to detect the difference between the null hypothesis $P = 0.5$ (Tricutan-treated side preferred) and a hypothetical improvement $P = 0.75$ for the Tricutan-treated side. A statistically significant difference is achieved if the difference from the null hypothesis reaches $P < 0.05$.

All adverse events, either observed by the investigators or reported by the patient spontaneously or in response to direct questioning, were noted in the source documents and in the adverse event section of the CRFs. The investigator assessed the adverse experiences, which were recorded with the time of onset, severity, and relationship to study medication, date of resolution, action taken and outcome of the adverse event.

## Results

Three women of the 28 included did not complete the 4-week treatment period. The reason for discontinuing was a mild irritative contact dermatitis. Three further women did not fill out the self-assessment form. Thus the results of the Reviscometer readings and clinical evaluation are based on the 25 women who completed the treatment period. The results of the self-assessment evaluation are based on the 22 women who completed the treatment period and filled out the self-evaluation form.

The measurements of shear wave propagation in the skin with the help of the Reviscometer analyses provide an objective way of determining skin firmness. At the start of the treatment there was no difference in Reviscometer reading between the half of the face to be treated with Tricutan and the part of the face to be treated with placebo (Table 1). After treatment for 4 weeks there was a significant difference ($P < 0.01$) between the readings of the Tricutan-treated part of the face and the placebo-treated part of the face (Table 1). Tricutan treatment resulted in mean readings that were more than 20 per cent lower than the readings obtained from placebo treatment. Thus Tricutan treatment resulted in significantly increased skin firmness as compared to placebo control.

The acute effect on skin firmness was analysed by taking Reviscometer readings before and 15 min after application of Tricutan and placebo gel in the women who had completed the 4 week treatment course. There was no acute effect of Tricutan that could be registered at Reviscometer analysis in these women (Table 2).

The women made a blind, subjective evaluation of the overall effect of the treatment on the two halves of the face at the end of the 4 week treatment period. This blind evaluation showed that the perceived effectiveness of Tricutan was significantly higher ($p < 0.02$) than the

**Table 1.** Effect on face skin firmness by treatment with Tricutan and placebo gels, split face, for 4 weeks as evaluated by measuring resonance running time, RRTM, with Reviscometer (arbitrary time units)

| Treatment | RRMT at the start of the treatment | RRMT after 4 weeks of treatment |
|---|---|---|
| Tricutan | 184±61 | 164±64[a] |
| Placebo | 183±67 | 210±73 |

Readings were made at the start of the treatment, and after treatment for 4 weeks. Mean values ±SD, $n = 25$.
[a]Tricutan vs. placebo: $P < 0.01$.

**Table 2.** Acute effect on face skin firmness by treatment with Tricutan or placebo gels, split face, as evaluated by measuring resonance running time, RRTM, with Reviscometer (arbitrary time units)

| Treatment | RRTM before the application | RRTM 15 min after the application |
|---|---|---|
| Tricutan | 164±64 | 164±58[a] |
| Placebo | 210±73 | 211±81[a] |

Readings were made on women previously treated for 4 weeks with Tricutan or placebo gels just before the application, and again 15 min after the application. Mean values ±SD, $n = 25$.
Tricutan vs. placebo: $P < 0.01$.
[a]Tricutan 15 min vs. Tricutan 0 min: $P > 0.5$. Placebo 15 min vs. placebo 0 min: $P > 0.5$.

**Table 3.** Overall clinical effectiveness of 4 weeks' treatment with Tricutan or placebo gels in improving skin quality as evaluated by the participating women (self evaluation, $n = 22$) or by the doctor (clinical evaluation, $n = 25$)

| | Tricutan | Placebo |
|---|---|---|
| Self evaluation | $4.0 \pm 1.7^{a}$ | $2.7 \pm 1.3$ |
| Clinical evaluation | $3.2 \pm 0.9^{b}$ | $2.0 \pm 0.7$ |

The evaluation was made on an 8-graded scale where 0 was deterioration, 2 no change, 4 somewhat improved, 6 clearly improved, and 8 excellently improved. Mean values $\pm$SD.

[a]Tricutan vs. placebo: $P<0.02$.

[b]Tricutan vs. placebo: $P<0.01$.

effectiveness of the placebo gel (Table 3). Also the doctor made a blind evaluation of the effect of treatment. Also this clinical evaluation showed that Tricutan resulted in a significantly better overall effect than placebo ($p<0.01$).

The adverse drug reactions to the treatment were limited. Three women withdrew from the trial because of mild irritative contact dermatitis. Several other women reported mild, temporary irritative reactions after 3–4 days. However, these reactions subsided and disappeared within a few days. No other adverse drug reactions were reported.

## Discussion

The most characteristic sign of old age is sagging skin and deep wrinkles. To combat signs of old age an important step would be to increase skin firmness and elasticity. For more than 20 years topical retinoids have been recognised for their efficacy in reversing these signs of photoageing of the skin. Topical retinoids constitute the present standard therapy for this condition. However, retinoids are not without serious side effects even at topical application, and are known to be teratogenic. Therefore other treatment modalities are sought for. This has led to the introduction in the over-the-counter market of an abundance of topical preparations alleged to combat the changes in ageing skin. Despite the media attention and consumer popularity that many of these preparations have attained, there have been few clinical investigations to support the claims for clinical efficacy (Chiu and Kimball, 2003; Glaser, 2004; Rona et al., 2004). Tricutan is such a topical preparation newly introduced in the market. The composition of this preparation is mainly based on empirical data. The clinical study of Tricutan reported here is the first step to document the clinical efficacy of this novel preparation.

The components of Tricutan, extracts of Rosmarinus officinalis (rosemary), Centella asiatica (gotu kola), tetrahydrocurcumin derived from Curcuma longa (tumeric), and DMAE, have been shown to inhibit destructive inflammatory processes in skin (Huang et al., 1991, 1994; Grossman, 2005), to reduce free radical-induced skin damage (Calabrese et al., 2001; Phan et al., 2001; Panchatcharam et al., 2006), to increase skin collagen synthesis (Panchatcharam et al., 2006), to increase skin tissue elasticity and firmness with possible involvement of underlying facial muscle tone (Uhoda et al., 2002; Grossman, 2005), and to improve wound healing (MacKey and Miller, 2003; Panchatcharam et al., 2006). Centella asiatica-extract, with its triterpenoids asiaticoside and madecassoside as major constituents, regulates the activity of fibroblasts which may explain its use for woundhealing, burns and eczema. Rosmarinus officinalis contains the antioxidant rosmarinic acid whereas the essential oil of this medicinal plant with its terpenoids cineol and borneol (acetate) has hyperaemic effects. The combined action of the components of Tricutan could be expected to have a beneficial effect on firmness in photoaged skin. The results of the present placebo-controlled, split-face study showed that in fact Tricutan had a clear, objectively demonstrated effect in improving skin firmness. Furthermore the positive effect could subjectively be recognised by the test individuals as well as by the investigating doctor. Earlier pilot experiments have suggested that an effect on skin firmness could be observed already within 1 h after application of Tricutan. The acute effect of Tricutan was also evaluated in the present study. However, no acute effect of Tricutan on skin firmness could be detected in these women who had been treated for 4 weeks. This does not rule out the possibility that an acute effect could have been registered at application to previously untreated women and to women who have had only short previous treatment.

The objective measurements of skin firmness were made with the help of a new device, the Reviscometer. With this device it is possible to measure the running time of acoustical shear wave propagation in skin. This reveals the mechanical properties of the epidermis and superficial dermis, and has found utility in several investigations already (Nizet et al., 2001; Uhoda et al., 2002; Uhoda and Pierard, 2003; Dang et al., 2005; Quatresooz et al., 2006). This device would appear to be a suitable tool for investigations not only of Tricutan but of any preparation which is claimed to alter skin elasticity and firmness.

Tricutan appears to be a preparation with obvious benefits in the treatment of ageing skin. The results of the present study make further studies of the clinical effectiveness warranted. Of high interest would be to investigate if Tricutan treatment could be used to delay the need for surgical face-lift and maybe slow down the development of skin carcinoma.

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