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Antipruritic Effect of Natural Superoxide Dismutase – Sensory Evaluation

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SUMMARY The primary objective of the study was to evaluate the antipruritic effect of natural superoxide dismutase in the cosmetic product Sodermix® cream. In this randomized intra-individual study including 15 volunteers, 14 female and one male, mean age 41±4 (range 18-66) years, the cosmetic product Sodermix® cream was evaluated according to the Dermscan Group protocol by recording thermal sensitivity levels using Cutaneous Thermal Sensitivity analyzer before and 30 and 90 minutes after the product application. The study was conducted from April to June 2008. Study results showed a decrease in the lengths of pruritus 30 minutes of the product application onto the treated zone and a significant decrease in pruritus intensity 90 minutes of the product application onto the treated zone. The study allows for evaluation of physical sensation and quantification of heat with cutaneous thermal sensitivity measurements as a psycho-physical method to evaluate variables of thermal sensations in relation to variables by thermal stimuli. The study demonstrated a significant antipruritic effect of Sodermix® cream.

KEY WORDS: pruritus, cutaneous sensitivity to thermal stimuli, natural superoxide dismutase, Sodermix® cream

INTRODUCTION

In humans there are three forms of superoxide dismutase (SOD) located in the cytoplasm (SOD_1), mitochondria (SOD_2) and extracellular space (SOD_3). SOD is used in cosmetic products to reduce free radical damage to the skin and pruritus in skin diseases. On many occasions, topical SOD has been observed to exert strong antipruritic activity. Pruritus can affect nearly all mammals and may present diagnostic challenge to the clinician. The aim of this study was to evaluate the antipruritic effect of the cosmetic product Sodermix® cream in volunteers. Sodermix® cream contains natural SOD, a patented vegetal active ingredient extracted from green tomato. The effect of the product was evaluated 30 and 90 minutes after its single standardized application.

The Cutaneous Thermal Sensitivity (CTS) measurement technique was employed to study physical sensations and for sensorimetric evaluation of the variables of thermal sensations in relation to variables of thermal stimuli (1,2), as well on C nerve fibers and on A delta nerve fibers (3).

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MATERIALS AND METHODS

This was a randomized, intra-individual study; each subject serving as his/her own control. CTS measurement was used to test sensory response to thermal stimuli and to quantify cutaneous sensitivity as a psycho-physical method for sensorimetric evaluation. This method allows for evaluation of physical sensation and quantification of the associated heat level. The perception of heat includes sensitive anatomical elements, principally corpuscle receptors and free terminal nerve fibers (1,2). The antipruritic effect was evaluated by recording thermal sensitivity levels felt by the subjects with the use of Thermal Sensitivity Analyzer (TSA^R) before and 30 and 90 minutes after the application of Sodermix® cream.

The antipruritic effect was determined by comparison of variations in the period of pruritus occurrence, its length and intensity before and after the application of the product *versus* placebo zone without any cream. The period of occurrence and length of pruritus are expressed in seconds, and intensity evaluated by the subjects as grade from 0 to 4. A probe is applied onto the predetermined zone on the wrists. The technician regularly increases the probe temperature (or ordered temperature). Four levels of thermal sensitivity are identified and announced by the subject with an automatic recorder system, followed by the subject's pressing the remote control for "identification of heat sensation" level: the subject identifies the thermal nature of the stimulus for the first time; "sensorial comfort" level: the subject feels a comfortable sensation of heat; "sensorial discomfort" level: the subject feels a sensation of heat which is uncomfortable but not painful; "pain" level: the indication of this sensation by the subject stops the thermal stimulus. The temperatures corresponding to the levels announced by the subject are directly recorded in a computer data file. The mean of the temperatures corresponding to the "sensorial discomfort" and "pain" levels, i.e. a temperature level that is more likely to induce pruritus, is programmed to be applied onto the measurement zone. The period of occurrence and length of pruritus reported by the subject are timed by the technician. The intensity of pruritus is evaluated by the subject on the following scale: none = 0; slight = 1; moderate = 2; severe = 3; and very severe = 4. The subject is included if he/she has pruritus for 240 seconds after the application of the sounding equipment. The measurements of the antipruritic effect are performed on two zones: one zone treated by the test product and a symmetric zone that is left untreated.

Measurements are performed on the study zone before treatment. After the application of the product, new measurements are done, according to the kinetics and function of the test product.

With the antipruritic action, one of the three conditions is observed: an increase in the period of pruritus occurrence; and/or a decrease in the length of pruritus; and/or a decrease in the intensity of pruritus. The TSA^R is used because it offers a standardized quantity of heat and skin surface temperature measurement is continuous during the study due to the probe.

The thermal probe device (3.2 cm in diameter) connected to the computer ensures precision of 0.05 °C, thermal regulation system, and going back directly to the basal temperature when the programmed temperature has proved effective. The TSA^R has a safety level (maximum temperature) and a cycle starting level of increasing temperature (32 °C).

Method pertinence

The method is used to test sensory response to thermal stimulus and to quantify cutaneous sensitivity. Contrary to other stimuli (e.g., chemicals), the product does not interfere with the measurement method. Comparison of measurement variations on a untreated zone suppresses the natural variability of cutaneous sensitivity during the measurement period.

Subjects

The study included 15 subjects. Inclusion criteria were general, i.e. good health status; informed consent in writing; cooperative subject; awareness of the necessity and duration of control visits so that perfect compliance with the protocol established by the clinical trial center could be expected; and specific criteria: female and male subjects over 18 years of age and subjects developing pruritus to a thermal stimulus.

Non-inclusion criteria were: pregnant or nursing women and women planning to get pregnant during the study; analgesics taken during the last 24 hours; cutaneous pathology on the study zone (eczema, etc.); use of topical or systemic treatment during the previous weeks, which could interfere with the assessment of cutaneous acceptability of the test product; excessive exposure to sunlight or UV-rays within the previous month; subjects enrolled in another clinical trial during the study period; subjects having sensorineural disorders; subjects suffering from chronic itch; subjects having taken anti-inflammatory drugs, antihistamines,

antidepressants, anxiolytics or tranquilizers within the previous month; and excessive use of tobacco or alcohol.

Compliance assessment

If the protocol was not respected and if the deviation was minor, the technician in charge of the study warned the subject of the importance of respecting the prescribed protocol. If the subject persisted or if the deviation was major, the subject was declared non-compliant. In this case, the subject was removed from the study for non-compliance.

Standardized application of the product was done at the laboratory, by the technician in charge of the study. During the study, no dermopharmaceutical or cosmetic product other than the study product was allowed to be applied on the hands. Excessive exposure to sunlight or UV-rays during the study was not allowed.

The subjects came to the laboratory without having applied any product onto the wrists since the previous evening and without having taken analgesics for the last 24 hours. They read, signed and dated the information sheet (instructions on the product use and restrictions related to the study) and informed consent forms in duplicate. These documents were also signed and dated by the person conducting the informed consent discussion. The subjects received a copy.

Two symmetric zones were determined on the inner aspect of the wrists. Identification of four levels of thermal sensitivity was done by the subject with an automatic recorder system, followed by pressing the remote control.

CTS stages were determined on the inner side of the wrist to identify the temperature level that was more likely to induce pruritus (a mean of „sensorial discomfort" and „pain" stages). After 15 minutes (t15) the probe was applied onto the wrist at the predefined temperature. The period of occurrence and length of pruritus reported by the subject were timed by the technician at 15 to 90 minutes of the Sodermix® cream application.

On D0 t0

The subjects came back to the laboratory without having applied any product to the wrists since the previous evening and without having taken analgesics for the last 24 hours.

Determination (D0) of two symmetric zones on the inner aspect of the wrists: one wrist to be treated by the product (Z1), and the other wrist that remained untreated (Z2). Measurement of pruritus on Z1=t0: occurrence period, intensity and length of pruritus.

On D0 t15

Measurement of pruritus on Z2=t0: occurrence period, intensity and length of pruritus.

On D0 t30

Standardized application of the study product onto the treated zone. The other wrist remained untreated.

On D0 t60

Measurement of pruritus on Z1 (t30 min after application), occurrence period, intensity and length of pruritus.

On D0 t75

Measurement of pruritus on Z2 (untreated), occurrence period, intensity and length of pruritus.

On D0 t120

Measurement of pruritus on Z1 (t90 min after application), occurrence period, intensity and length of pruritus.

On D0 t135

Measurement of pruritus on Z2 (untreated), occurrence period, intensity and length of pruritus. Ambient conditions during measurements: room temperature: 24±2 °C; relative humidity between 40% and 60%.

An Adverse Event is defined as any expression of noxious and unwanted symptom in subjects taking part in biomedical research, whether or not it is related to the study product(s).

A Serious Adverse Event (SAE) is defined by one of the following criteria: death, life threatening, hospitalization, persistent or significant disability or incapacity, congenital anomaly, overdose, cancer, and other event considered clinically significant by the investigator.

All Adverse Events related to the study product (adverse effect) were reported in the Case Report Form (CRF) and study report.

All concomitant treatments were reported in the CRF and study report.

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All SAEs were reported in the CRF and study report.

All Adverse Effects were transmitted by fax or e-mail to the sponsor within 48 hours of information on their occurrence (according to the investigator's advice). All SAEs were transmitted by fax to the sponsor within 24 hours of information on their occurrence and then confirmed by mail within 48 hours.

When an Adverse Effect persisted at the end of the study, the Investigator ensured that the subject was followed up until total resolution without taking off the application of the obligations and the responsibilities of the sponsor.

Study exit conditions

In compliance with the Good Clinical Practice (GCP), Helsinki Declaration (1964) and its successive updates, and with the French act 2004-806 dated August 9, 2004 concerning public health (4-6), subjects had the right to exit from the study at any time and for any motive. The investigator could also have interrupted the subject participation in the study prematurely in case of an intercurrent disease or adverse effect. The sponsor could have demanded that any subject be excluded from the study for major infringements of the protocol, for administrative reasons or any other motive. Nevertheless, premature removal of a high percentage of subjects from the study could have made the study difficult or impossible to interpret. Consequently, any premature exit without valid motives should have been avoided as much as possible and was carefully documented in the case report form, the final report and if necessary in the Adverse Event form. Every premature exit must have been classified under one of the following headings: Adverse Event Occurrence; Serious Adverse Event Occurrence; withdrawal of consent; untraceable panelist; occurrence of non-inclusion criteria; non-adherence to the protocol; and other reason.

No replacement was anticipated as 10% of additional subjects were planned to be included in the study.

Data collection and validation were performed according to the "*Informatique et libertes*" act (7), an identification code was attributed to each subject to keep his/her identity confidential. This code consisted of the three first letters of the subject's name and the two first letters of his/her first name. The personnel in charge of the study (technician, physician, etc.) added data to the subject case report form and to the computerized database. Data were validated by Dermscan's study manager.

An audit and/or trial monitoring visit might be carried out at the sponsor's request or by the appropriate regulatory authority, to verify that the study was conducted according to the determined protocol and current regulations.

Quality assurance and quality control

In order to ensure the conformity of clinical trials to the study sponsor's requirement, the Dermscan Group has implemented a quality management system that has been certified ISO 9001:2000 by the A.F.A.Q. organization since 2002. This quality assurance system includes GCP and regulation requirements. Each study report is subjected to quality control by a member of the Dermscan Proofreading Committee. The proofreader has been chosen because he (she) is not involved in the audited study. The inspection of the study report allows for confirming that the results reflect exactly the study raw data. A certificate of quality control signed by the person who checked the report is enclosed in each study report to certify that the study report reflects the study raw data and fulfils any standard and regulatory requirements.

Confidentiality procedure: the product supplied by the sponsor was encoded. Before the beginning of the study, the product was kept at room temperature in a dedicated air-conditioned room. This room is locked and access controlled.

The Sodermix® cream, a white cream in a tube, was applied at 2 µL/cm^2 onto the wrist with light, uniform massage with a fingerstall. The application zones of the study products were randomized according to the list presented in Appendix 1. All study subjects tested the same product.

Data analysis – calculation formulas

Raw variations (Δ) and their percentage (Δ%) for the study parameters were calculated according to the following formulas:

$$\Delta = (TZ_{ti} - TZ_{t0})$$

$$\Delta\% = \left(\frac{TZ_{ti} - TZt0}{TZ_{t0}}\right) \times 100$$

where

TZ = value obtained on the treated zone(s)

t0 = before application

ti = at each measurement time after application

The percentage of variation (Δ%) is expressed as percentage of variation on the measurement

Table 1. Characteristics of study subjects

Subject No.	Last name	First name	Age	Sex	Skin type	Phototype	Inclusion date	End date
1	FOR	PA	46	F	D	I	4/24/2008	5/2/2008
2	MER	SA	18	F	C	I	4/24/2008	5/2/2008
3	BEN	HA	31	F	D	IV	4/29/2008	5/6/2008
4	MUR	MU	40	F	N	II	4/30/2008	5/7/2008
5	PIA	AN	66	F	D	III	5/19/2008	5/21/2008
6	DUF	CH	31	F	N	II	5/14/2008	5/21/2008
7	BOU	MI	50	F	D	III	5/19/2008	5/26/2008
8	COL	OD	57	M	B	III	5/19/2008	5/26/2008
9	BIO	FR	43	F	D	III	6/3/2008	6/4/2008
10	BOU	SY	66	F	D	III	6/3/2008	6/4/2008
11	SAL	ZA	35	F	D	III	6/3/2008	6/6/2008
12	GAR	SI	30	F	C	IV	6/10/2008	6/13/2008
13	LAA	OU	28	F	D	III	6/10/2008	6/11/2008
14	KOL	IR	44	F	C	I	6/12/2008	6/13/2008
15	PET	CE	26	F	D	III	6/23/2008	6/24/2008
	Mean		41	F 14	N 3	I 3		
	Median		40	M 1	C 3	II 2		
	Minimum		18		G 0	III 8		
	Maximum		66		D 9	IV 2		
	SEM		4			V 0		
	95% CI		8			VI 0		

Legend: F: female; M: male; N: normal skin; C: combination skin; G: greasy skin; D: dry skin

zone (TZ_{ti}-TZ_{t0}). These variations are balanced against the initial value TZ_{t0} (before application). Thus, this expression (Δ%) gives the variation, in percentage, on the measurement zone compared to the initial conditions (TZ_{t0}).

The measured values are presented in raw value tables. These tables also show descriptive statistics: means, medians, minima, maxima, standard errors of the means (SEM) and 95% confidence intervals (95% CI).

Also, raw variations, percentage variations, descriptive statistics (8) and results of statistical analysis (p) are presented in variation tables (1-10).

Statistical method

Statistical analysis determined the significance of variations obtained under the action of test products. The values obtained on the zone treated by the products were compared with those recorded on the untreated zone at each time of kinetics. Data were analyzed by use of paired t-test. This method tests whether the mean of sample differences between pairs of data is significantly different from the hypothetical mean, zero under the null hypothesis (H0). The alternative hypothesis (H1) was that the average difference was either greater or less than 0 (two-tailed test). Before carrying out a test, a type I error of 5% was chosen (which corresponds to the risk of rejecting a true null hypothesis).

→ If p≤0.05, H0 was rejected. There was a significant difference between the zones or between each time of kinetics. → If p>0.05, the mean was not different from 0. Data did not show significant

APPENDIX 1. Randomized side

Subject No.	Treated zone	Untreated zone
1	L	R
2	L	R
3	R	L
4	R	L
5	L	R
6	L	R
7	L	R
8	R	L
9	L	R
10	R	L
11	L	R
12	L	R
13	R	L
14	R	L
15	R	L

R: right side;
L: left side

difference between the zones or between times of kinetics. The Excel 9.0 version 2000, SPSS 15.0 for Windows statistical software was employed.

All documents relating to this study have been kept for one year at the most at Dermscan Group before being referred to the Locarchives company (Parc industriel de la plaine de l'Ain, Allée des cèdres, 01150 Saint-Vulbas, France).

RESULTS

Subject characteristics are shown in Table 1.

On the product application side, 33% and 20% of study subjects did not develop pruritus 30 and 90 minutes of product application, respectively. Only the subjects that developed pruritus are included in the results shown below.

Tables 2, 3 and 4 present a synthesis of the variations observed (means ± SEM) in the period of occurrence, length and intensity of pruritus on the zone treated by Sodermix® cream *versus* untreated zone.

Table 2. Onset of pruritus (in seconds)

	Treated zone	Untreated zone	Δ(TZ-NTZ)	p value	Significance
t0	84±14	67±13			
t30	111±20	72±14			
t90	112±17	87±16			
Δ(t30-t0)	45±18	9±11	35±15	**0.040**	**YES**
Δ(t90-t0)	35±23	27±16	7±32	0.826	NO

Sodermix® cream significantly delayed the onset of pruritus 30 minutes of the application; pruritus appeared 35 seconds (mean) later on the treated zone (p=0.040).

Table 3. Length of pruritus (in seconds)

	Treated zone	Untreated zone	Δ(TZ-NTZ)	p value	Significance
t0	152±13	171±13			
t30	103±21	151±19			
t90	111±19	141±20			
Δ(t30-t0)	-65±19	-23±10	-41±17	**0.042**	**YES**
Δ(t90-t0)	-46±18	-37±16	-8±28	0.768	NO

Sodermix® cream significantly decreased the length of pruritus 30 minutes of the application; the length of pruritus was reduced by 41 seconds (mean) on the treated zone (p=0.042).

Table 4. Intensity of pruritus

	Treated zone	Untreated zone	Δ(TZ-NTZ)	p value	Significance
t0	3±0.1	2±0.2			
t30	2±0.3	2±0.2			
t90	1±0.1	2±0.3			
Δ(t30-t0)	-1±0.2	0±0.4	-1±0.5	0.239	NO
Δ(t90-t0)	-1±0.1	-1±0.4	-1±0.4	**0.026**	**YES**

Sodermix® cream significantly decreased the intensity of pruritus 90 minutes of the application; the intensity of pruritus was less pronounced (-1±0.4) on the treated zone (p=0.026).

In the subjects that presented pruritus after the application of the study product application, we observed a significant and favorable increase in the time to pruritus onset and a significant and favorable decrease in the length of pruritus 30 minutes after the application, in comparison to both the initial values and to the untreated zone.

In the subjects that presented pruritus after the application of the product tested, a significant and favorable decrease in the intensity of pruritus was recorded 90 minutes after the application, in comparison to both the initial values and to the untreated zone (Table 4).

Figures 1-3 show the three parameters evaluated: period of occurrence, length and intensity of pruritus.

Fig. 1. Onset of pruritus : treated zone *versus* untreated zone (in seconds).

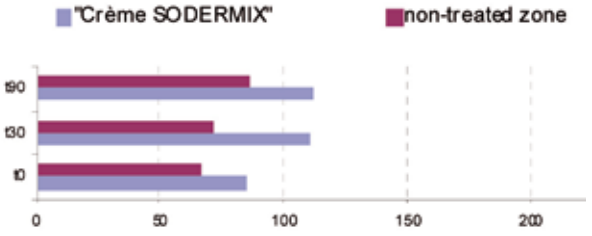


Fig. 2. Length of pruritus: treated zone *versus* untreated zone (in seconds).

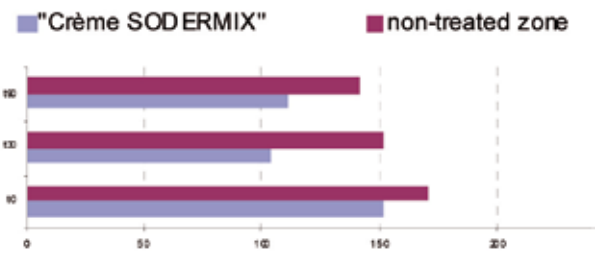
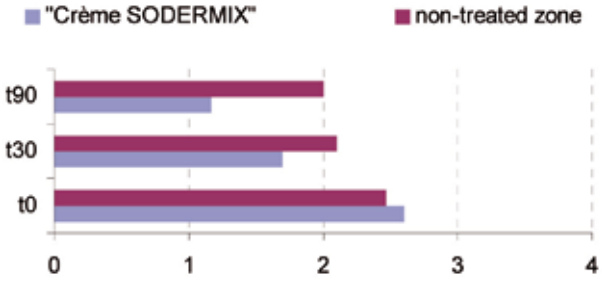


Fig. 3. Intensity of pruritus: treated zone *versus* untreated zone.



Scale for the intensity of pruritus: none = 0; slight = 1; moderate = 2; severe = 3; very severe = 4

Variations in the onset of pruritus are shown in Tables 5 and 6.

Table 5. Onset of pruritus t30 minutes

Onset of pruritus t30 minutes			
Subject No.	**Untreated zone**	**Treated zone**	**% of variation in onset of pruritus t30 min compared with untreated zone**
1	64	139	117
2	0	0	(NA)*
3	82	15	-82
4	(NA)*	(120)+	(NA)*
5	62	48	-23
6	158	105	-34
7	(NA)*	(207)*	(NA)*
8	(NA)*	(76)*	(NA)*
9	(NA)*	(165)*	(NA)*
10	(NA)*	(81)*	(NA)*
11	114	64	-44
12	199	129	-35
13	87	79	-9
14	165	50	-70
15	177	91	-49
Mean	110.8	72	**-25**

(NA)* = not applicable, values not included in data analysis

Table 6. Onset of pruritus t90 minutes

Onset of pruritus t90 minutes			
Subject No.	**Untreated zone**	**Treated zone**	**% of variation in onset of pruritus t90 min compared with untreated zone**
1	139	138	-1
2	10	0	-100
3	55	22	-60
4	(NA)*	(133)*	(NA)*
5	239	127	-47
6	118	139	18
7	(NA)*	(182)*	(NA)*
8	(NA)*	(67)*	(NA)*
9	51	195	282
10	124	78	-37
11	132	82	-38
12	123	45	-63
13	74	80	8
14	123	61	-50
15	161	71	-56
Mean	112.4	86.5	**-12**

(NA)* = not applicable, values not included in data analysis

The length of pruritus is presented in Tables 7 and 8.

Table 7. Length of pruritus t30 minutes

Length of pruritus t30 minutes			
Subject No.	**Untreated zone**	**Treated zone**	**% of variation in length of pruritus t30 min compared with untreated zone**
1	40	42	5
2	240	240	0
3	225	158	-30
4	(120)*	(0)*	(NA)*
5	85	50	-41
6	135	82	-39
7	(33)*	(0)*	(NA)*
8	(164)*	(0)*	(NA)*
9	(75)*	(0)*	(NA)*
10	(159)*	(0)*	(NA)*
11	176	126	-28
12	111	41	-63
13	161	153	-5
14	190	75	-61
15	149	63	-58
Mean	151.2	103	**-32**

(NA)* = not applicable, values not included in data analysis

Table 8. Length of pruritus t90 minutes.

Length of pruritus t90 minutes			
Subject No.	**Untreated zone**	**Treated zone**	**% of variation in length of pruritus t90 min compared with untreated zone**
1	66	42	-36
2	240	230	-4
3	218	185	-15
4	(107)*	(0)*	(NA)*
5	81	1	-99
6	20	32	60
7	(58)*	(0)*	(NA)*
8	(173)*	(0)*	(NA)*
9	45	140	211
10	162	116	-28
11	158	108	-32
12	195	117	-40
13	160	166	4
14	179	117	-35
15	169	79	-53
Mean	141.1	111.1	-6

(NA)* = not applicable, values not included in data analysis

The intensity of pruritus is shown in Tables 9 and 10.

Table 9. Intensity of pruritus t30 minutes

Intensity of pruritus t30 minutes			
Subject No.	**Untreated zone**	**Treated zone**	**% of variation in intensity of pruritus t30 min compared with untreated zone**
1	1	1	0
2	2	3	50
3	3	1	-67
4	(2)*	(0)*	(NA)*
5	2	2	0
6	1	2	100
7	(3)*	(0)*	(NA)*
8	(3)*	(0)*	(NA)*
9	(1)*	(0)*	(NA)*
10	(1)*	(0)*	(NA)*
11	3	1	-67
12	3	3	0
13	2	2	0
14	2	1	-50
15	2	1	-50
Mean	2.1	1.7	0

(NA)* = not applicable, values not included in data alysis

Table 10. Intensity of pruritus t90 minutes

Intensity of pruritus t90 minutes			
Subject No.	**Untreated zone**	**Treated zone**	**% of variation in intensity of pruritus t90 min compared with untreated zone**
1	1	1	0
2	3	2	-33
3	3	1	-67
4	(2)*	(0)*	(NA)*
5	1	1	0
6	1	1	0
7	(3)*	(0)*	(NA)*
8	(4)*	(0)*	(NA)*
9	1	1	0
10	1	1	0
11	3	1	-67
12	4	2	-50
13	2	1	-50
14	2	1	-50
15	2	1	-50
Mean	2	1.2	**-31**

(na)* = not applicable, values not included in data analysis

DISCUSSION

The present study demonstrated antipruritic effect of Sodermix® cream, measured by use of the cutaneous thermal sensitivity analyzer. The antipruritic effect of Sodermix® cream was sensorily evaluated in detail by TSA^R. The study was in compliance with GCP, Helsinki Declaration (1964) and French act 2004-806 (2004 and 1978). A significant antipruritic effect was demonstrated 30 minutes and 90 minutes of the Sodermix® cream application, in comparison to the initial values and to the untreated zone. This effect was characterized by a decrease in the number of subjects that developed pruritus and in the length of pruritus following application of the study product; a significant increase in the time to the onset of pruritus (in subjects that developed pruritus) on the treated zone 30 minutes of the application; and a decrease in the intensity of pruritus (in subjects that developed pruritus) on the treated zone 90 minutes of the application.

The antipruritic effect of SOD acts upon NK-1 receptors, various proinflammatory cytokines, calcitonin gene-related peptide, down-regulation of TNF-α and suppression of nitric oxide production, as presented in this study and supported by literature data (9).

CONCLUSION

The aim of the study was to evaluate the antipruritic effect of natural SOD contained in the cosmetic product Sodermix® cream 30 and 90 minutes after application in study subjects. Previous encouraging results reported with topical SOD should have a scientific basis to explain its efficacy. According the results of this study, we demonstrated the antipruritic effect of the cosmetic product Sodermix® cream, which could prove useful for local supportive therapy of pruritogenic dermatoses.

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