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Adhesiveness of a new testosterone-in-adhesive matrix patch after extreme conditions

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ABSTRACT

The objective of the study was to evaluate the adhesiveness of a new thin, transparent and comfortable testosterone-in-adhesive matrix patch, Testopatch®, after extreme conditions. The study was a single-centre, open-label with randomization of sites (upper arms, lower back, thighs) and sides (left, right) of two 45 cm^2 patches, in 24 healthy subjects. Patches were symmetrically applied on one of the three sites. One patch was removed after 2.0 h, under resting conditions and the other patch was removed at 3.5 h, after extreme conditions (physical exercise, sauna, whirl bath). Adhesiveness was assessed of the area stuck and the measure of the forces necessary for patch removal using a Peel Patch Tester™. Local safety was assessed at 2.0 and 3.5 h. After physical exercise and after sauna, patch adhesiveness was excellent (95%) when applied on the thigh and very good (90%) on the upper arm. Forces of patch removal were significantly lower at 3.5 h than 2.0 h, and at the lower back compared to the other application sites. There were no adverse effects. Slight erythema was observed that was considered to be clinically insignificant. Testopatch® was safe and displayed adhesiveness, compatible with physical activities.

1. Introduction

Transdermal drug delivery systems are widely used for a variety of indications including chronic pain, hypertension, nicotine replacement therapy and hormone replacement therapy (Burkman, 2007). Testosterone replacement therapy is a key issue for the management of hypogonadism, attenuating the effects of testosterone deficiency on sexual function, energy and mood (Burris et al., 1992; Bhasin, 1992; Meikle et al., 1996; Arver et al., 1996; Snyder et al., 2000).

The *Institut de Recherche Pierre Fabre* (*IRPF*), has developed a testosterone-in-adhesive transdermal patch (Testopatch®) with three different strengths of 1.2, 1.8 and 2.4 mg/day to accommodate inter-individual difference in testosterone requirements of hypogonadal men with the aim to overcome the following limitations in testosterone delivery of existing formulations (1) skin irritation with reservoir patches, (2) potential transfer to partner with gels, (3) "rolling waves" in testosterone levels, with parenteral testosterone esters, and (4) wide fluctuations and liver toxicity over time, with oral formulations (Korenman et al., 1987; Matsumoto, 1994; Wang et al., 2000; Swerdloff et al., 2000; Chik et al., 2005).

Testopatch® is used for 48 h, two patches being applied every other day to intact, non-scrotal skin, e.g. arms, lower back/upper buttock, or thighs with no skin reactions or only minimal erythema. According to the pharmacokinetic profile of the patch, patch application resulted in dose proportional increases in serum testosterone levels in hypogonadal men into the low to mid-normal range within the first hours and achieved steady state during 48 h (Raynaud et al., 2008a). Clinical studies demonstrated the efficacy of the patch to maintain constant physiological levels of sexual hormones over time.

The patch requires no specific precaution of use and was reported to be convenient and well accepted by the patients (Raynaud et al., 2008b). Treatment compliance by the patient is the key issue to get a stable restoration of testosterone levels. One of the most important criteria for the compliance, by the transdermal route, is the adhesiveness of the patch, especially during activities leading to sweating, wetting and watering.

Most of the studies with regard to the transdermal systems are dealing with drug delivery, pharmacokinetic and safety but few studies investigated the adhesiveness of the patches (Erianne and Winter, 1997; Padula et al., 2007; Maillard-Salin et al., 2000). The objectives of the present study were to assess the adhesiveness of

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Testopatch® after extreme conditions of sweating (physical exercise, sauna) and water immersion (whirl bath), by the evaluation, after each test, of the area stuck, the measurement of the forces necessary for patch removal, and skin reactions.

2. Materials and methods

2.1. Subjects

Twenty-four healthy male volunteers were included in the study and treated with Testopatch® (45 cm^2). Men with acute or chronic disease; history of hormone dependent cancer; known acute or chronic prostate pathology (prostate-specific antigen (PSA) >2 ng/ml); generalized dermatological disorder which could interfere with the study; history of allergy to patches or hypersensitivity to components of the study drug; inability to practice physical exercise, sauna and whirl bath; participating in another study, presently or during the previous 12 months; taking topical drug before the visit, were excluded.

Subjects were selected within 1 week before inclusion, after a complete medical examination, e.g. vital signs and physical examination, including the type of the skin. All subjects registered in the National Register of Volunteers of the French Ministry of Health and affiliated to health insurance, signed a written informed consent. This study was performed in accordance with Declaration of Helsinki concerning medical research in humans, Good Clinical Practice guideline (CPMP/ICH/135/95); French law (*Loi Huriet* 88-1138, December 20, 1988), and the European directive 91/507/EEC. The study was approved on January 12th, 2007 by the Local Independent Ethics Committee of Sud-Ouest, in France.

2.2. Materials

Testopatch® is an oval adhesive-based matrix patch comprising a polyester, transparent backing film that provides protection, ensures impermeability and allows the patch to stick closely to the skin, a siliconized polyester removable liner film, and in between, an adhesive matrix containing testosterone (0.5 mg/cm^2) and excipients (diethyl-toluamide, polyvinyl pyrolidone).

One patch delivers 0.04 mg/cm^2/day (calculated by a patch return testosterone content analysis over a two days application period) and is available in three dosages of 1.2, 1.8 and 2.4 mg/day for an area of 30, 45 and 60 cm^2, respectively. The dosage used in this study was 45 cm^2 (Fig. 1).

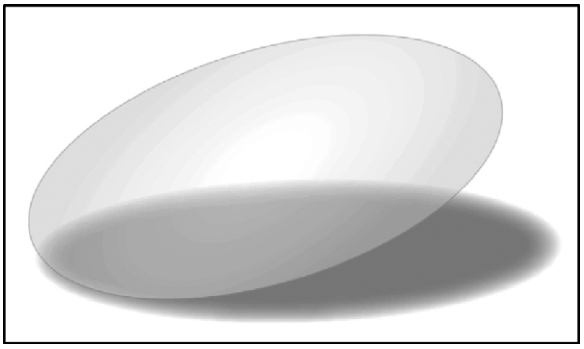

Fig. 1. Photography of Testopatch 45 cm^2 comprising an oval adhesive-based matrix patch with a polyester, transparent backing film, a siliconized polyester removable liner film, and in between, an adhesive matrix containing testosterone (0.5 mg/cm^2) and excipients (diethyl-toluamide, polyvinyl pyrolidone).

2.3. Study design

The study design was a single-centre, open-label, randomized, three sites (upper arms, lower back, or thighs) and two sides (left or right body half) of patch application.

Just before patch application, the skin had to be clean, dry and neither damaged nor irritated. Electric shaving, chemical depilatories and any other topical products including unguents or lotions, were to be avoided. At t_0, two patches were randomly assigned to be symmetrically applied by the same investigator, on one application site out of three (upper arms, lower back, thighs).

At t = 2.0 h, after resting, the outline of the patch area stuck was determined and the corresponding surface was evaluated. If patch detachment was >20%, the subjects were to be retested or the treatment discontinued, depending on the objective reason of detachment, i.e. type of skin or wrong application (Ehrlich et al., 1999). If patch detachment was ≤20%, removal of the first patch was performed according to the side of randomization with the Peel Patch Tester™ and, mean and maximal (±SEM) forces of removal were measured. The second patch was left on the other side, for the three consecutive tests.

At t = 2.5 h, subjects were placed in extreme conditions. They performed 15 min physical exercise (home bicycle), then 10 min sauna at 40 °C and finally 20 min whirl bath at 32 °C, with resting time after each test of 5–10 min, to allow the intermediate patch area stuck to be evaluated.

At t = 3.5 h, after the three consecutive tests, the area still stuck and the mean and maximal forces of removal of the second patch, were measured.

One patch, not correctly applied, detached from the thighs when the subject put on his trousers, and another patch was stuck to the interior of the sachet due to a partially peeled-off release liner. The investigator used the first two treatment units of the second series and applied these patches to the two patients. This allocation of replacement patches lead to the following randomized distribution to application sites, nine to upper arms, nine to lower back and six to thighs.

2.4. Evaluation of patch area stuck

The outline of the patch area stuck was hand-drawn using a black pen on a transparent foil and digitalized using a scanner. The surface covered by the black contour was determined, The area within the outline was filled in black, and the entire resulting surface was measured by automatic counting of the number of black pixels, followed by conversion of the latter into metric units on the basis of a calibration performed using a ruler included in the picture. The area determined at each time-point was calculated as a percentage of the total surface (45 cm^2). The above procedure was pre-validated by scanning ten times a 45 cm^2 surface. A mean result of 44.80 cm^2 (±0.26 cm^2) was obtained, underlining the high level of accuracy of the developed procedure.

2.5. Patch removal measurements

The Peel Patch Tester™ (Liorzou et al., 2000) is a portable apparatus to measure *in situ* the adhesiveness of a transdermal patch. It comprised an electric motor, a carry handle, a hook for fixing the patch, three "holding" sensors positioned on the handle and one sensor designated to measure the "peeling force" of the unit. The patch is fixed to a clip and subjected to a peeling movement with standardized speed (300 mm/min) and inclination (α = 135°). The front peel speed (V) is proportional to the speed lift (V') through the relation $V = V'/\sqrt{2}(1 - \cos\alpha)$. Analogue measurements registered by the sensors were first amplified, converted digitally to calculate the

mean, maximal, and minimal forces that were expressed in Newton (N) (Liorzou, 2000).

2.6. Safety assessments

Local safety was assessed 15 min after patch removal, at $t = 2.0$ h and $t = 3.5$ h by each subject, on any subjective signs of itching, burning sensations, tension or discomfort and, by the investigator, according to the Food and Drug Administration 7-item rating scale (0 = no evidence of irritation; 1 = minimal erythema, barely perceptible; 2 = definite erythema, readily visible; 3 = erythema and papules; 4 = definite edema; 5 = erythema, edema and papules; 6 = vesicular eruption; 7 = strong reaction spreading beyond test site). At the end of the three consecutive tests, a final clinical examination was performed and the investigator recorded any adverse effect observed and/or spontaneously reported by the subject. All results with regard to safety were exploratory and considered within a descriptive perspective.

2.7. Statistical analysis

The statistical analysis was performed on the intention to treat (ITT) population defined by subjects having received the treatment and completed the study. For quantitative variables, the following descriptive statistics were calculated: subjects/populations (N), mean, standard deviation (SD), minimum and maximum. For qualitative variables, frequency and percentage (%) were calculated. Drop-outs were considered only for the analysis of safety, since subjects were retested in case of a patch detachment >20%, at $t = 2.0$ h. The method based on the "Last Observation Carried Forward" (LOCF) was used for subjects with a total detachment of the patch before $t = 3.5$ h; in this case, the value "0" was taken into account on the times following the detachment until $t = 3.5$ h.

For adhesiveness, the area stuck was analysed using a paired Student's t-test or a paired Wilcoxon signed rank test, and subjected to a three-way analysis of variance (ANOVA) testing for time, sides and application sites. All results were presented as the mean ± SD and significance levels were set at $p < 0.05$ and $p < 0.001$.

3. Results

All randomized subjects ($N = 24$) were treated with Testopatch® and completed the study.

Subjects were aged 32.9 ± 9.4 years, with a weight of 73.2 ± 9.7 kg, height of 176 ± 7 cm, and a body mass index of 23.6 ± 2.6 kg/m^2. The sub-analysis by application site showed that all demographic parameters were well balanced across the three randomization groups.

3.1. Adhesiveness

After 2 h of patch application in resting condition, the area stuck was not different between the two sides. For the patches applied, on the left side, 92.66 ± 5.60% of the patch area was stuck compared to 92.69 ± 3.80% on the right side. A significant global difference was observed between the three application sites ($p = 0.02$). A significant global difference was observed between the three application sites ($p = 0.02$). A significant difference for the area stuck was observed between patches applied to the arms (90.35 ± 5.70%) and those applied to the thighs (96.28 ± 1.05%) ($p < 0.0062$). No difference was observed between the patches applied to the lower back (92.59 ± 2.76%) and those applied to the arms ($p < 0.08$) and the thighs ($p < 0.17$).

The area of the patch stuck was measured after the three consecutive tests, e.g. physical exercise, sauna and whirl bath, in the total population (Fig. 2). After 3.5 h of patch application in extreme condition, the area stuck was not different between the two sides. In the total population, there was a highly significant global decrease ($p < 0.0004$) of the patch area stuck at $t = 2.0$ h after resting *versus* $t = 3.5$ h after the three consecutive tests. At the end of the trial, >75% of the initial patch area still remained stuck to the skin. However, no significant difference of the patch area stuck was found after physical exercise and, after physical exercise followed by sauna, compared to the value at $t = 2.0$ h.

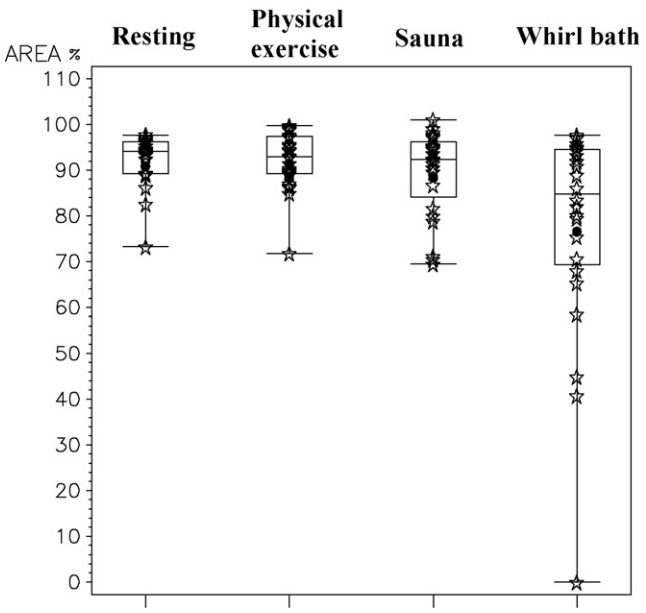

Fig. 2. Patch area stuck, after the three consecutive tests, in the total population ($N = 24$). The areas stuck were determined, after resting and the three consecutive tests, e.g. physical exercise, sauna, whirl bath. Results are expressed in percentage of total surface (45 cm^2) and represented by a combined box/scatter plot, with mean values represented by open squares and median values by lines.

The highly significant difference between sites ($p < 0.0001$), times ($p < 0.0001$), and the significant interaction between these two factors ($p < 0.001$) argued for the importance of the application site on the evolution of patch adhesiveness over the duration of the study.

The "lower back" was the only patch application site that displayed, after the whirl bath, a highly significant change of the area stuck overtime ($p < 0.0001$), compared to arm ($p < 0.002$) and thigh ($p < 0.2$). The area stuck was lowest with patches applied on the back (59.72 ± 28.25%), compared to arm (84.43 ± 9.37%) and thigh (95.33 ± 1.69%) (Fig. 3). The lowest value obtained on the lower back was attributable to one complete patch detachment in this group, included as 0% in the statistical analysis.

3.2. Forces of removal

Mean and maximal forces necessary for patch removal significantly decreased at $t = 3.5$ h, after the three consecutive tests, compared to $t = 2.0$ h after resting ($p < 0.0001$), in the total population and for all application sites ($p < 0.0001$) (Fig. 4). The mean force decreased from 7.5 ± 1.4 to 4.3 ± 1.7 N on the arm, from 9.1 ± 1.7 to 2.9 ± 1.6 N on the lower back and from 10.4 ± 3.9 to 5.6 ± 2.6 N on the thigh. The maximal forces of removal decreased from 8.85 ± 1.45 to 5.48 ± 1.89 N on the arm, from 10.637 ± 1.885 to 3.896 ± 2.021 N on the lower back and from 12.168 ± 4.613 to 7.013 ± 3.315 N.

The lower back was particularly affected by the conditions of the experimentation showing a significant difference in mean force of removal in comparison to arm ($p < 0.03$) and thigh ($p < 0.01$) and,

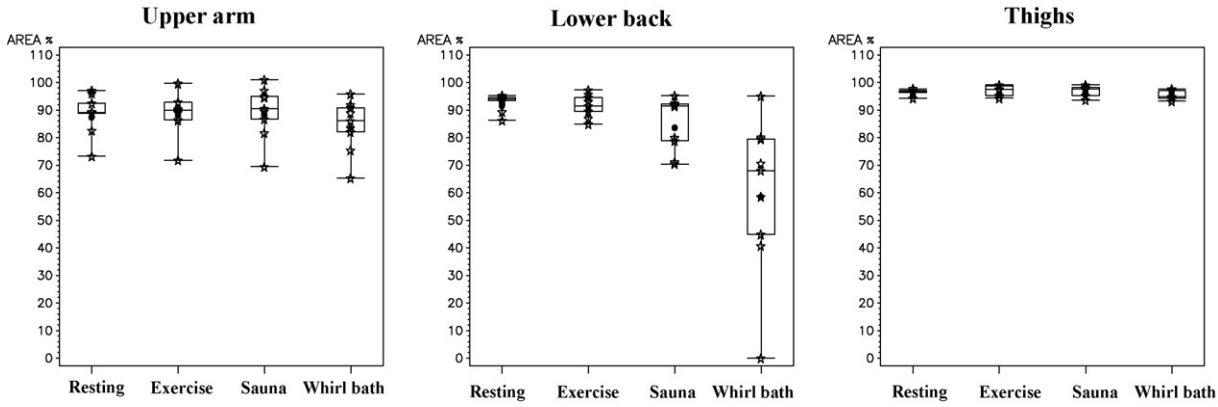

Fig. 3. Patch area stuck after the three consecutive tests, by application sites. The areas stuck on different application sites, arm, lower back and thigh, were estimated after each test, expressed in percentage of total surface (45 cm^2) as a mean ± SD and, represented by a combined box/scatter plot, with mean values represented by open squares and median values by lines.

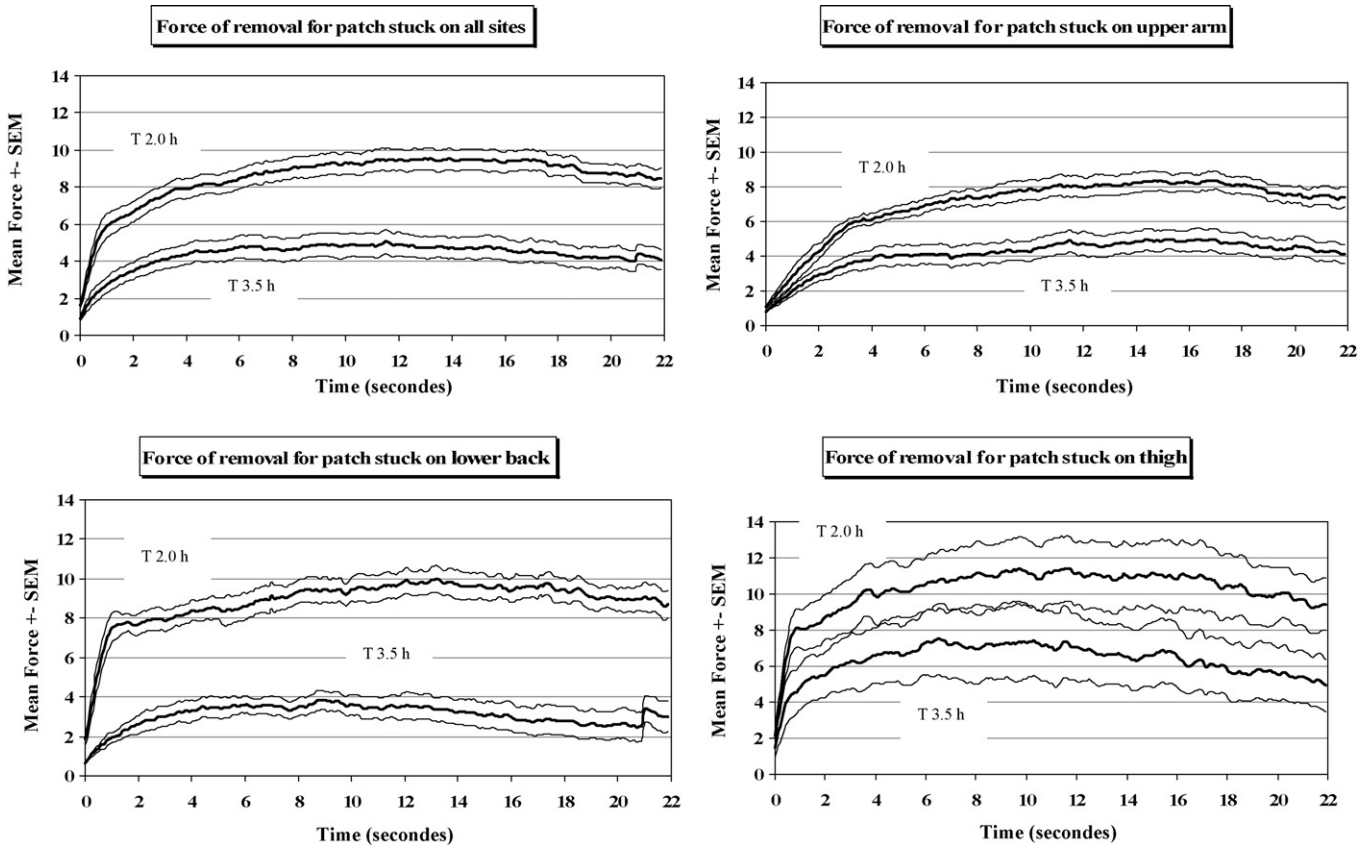

Fig. 4. Mean and maximal forces of patch removal on all sites and each application site, e.g. arm, lower back and thigh, over time. Results were expressed as mean forces (bold line) ± SEM (thin line) expressed in Newton.

in maximal force of removal in comparison to arm ($p < 0.001$) and thigh ($p < 0.02$). There was no significant difference in forces of removal between arm and thigh. Thus, measurement of removal forces was a valuable predictor for the evolution of patch area stuck.

3.3. Safety assessments and adverse effects

Skin irritation was evaluated 15 min after patch removal, at $t = 2.0$ h and $t = 3.5$ h, after resting and after the three consecutive tests, respectively. Eight percent (8.3%) and 16.7% of the subjects had no erythema, whatever the time of patch removal. A barely perceptible erythema was experienced by 75% and 79.2% of the subjects after the first ($t = 2.0$ h) and second ($t = 3.5$ h) patch removals, respectively. A readily visible erythema was observed on four subjects (16.7%) and only one subject (4.2%), after the first ($t = 2.0$ h) and second ($t = 3.5$ h) patch removals, respectively. No adverse effects were reported during the entire study.

4. Discussion

The present study assessed the adhesiveness of Testopatch®, after extreme conditions of sweating (physical exercise, sauna)

and water immersion (whirl bath) that could be encountered by patients, in life activities. The randomization of the patches to sides (left *versus* right) and the time of patch removal ($t = 2.0$ h or $t = 3.5$ h) from the body halves had no influence on the evolution of patch area stuck. At $t = 2.0$ h, the patch adhesiveness was different between the three application sites (arm < lower back < thigh). The maximal patch removal forces were significantly lower at the end of the three consecutive tests, with a significant difference between the lower back and the two other application sites.

At the end of the trial, patch adhesiveness significantly decreased in the total population, suggesting that at least, one of the tests is responsible for the observed decrease. However, neither physical exercise (home bicycle; 15 min) nor the combination of physical exercise plus sauna (40 °C, 10 min) had a significant effect on adhesiveness; the area stuck is similar (>90%). In contrast, patch adhesiveness on the lower back proved to be significantly sensitive to the effects of the whirl bath. The significant decrease to 75% in patch area stuck was observed after whirl bath, in the group assigned to patch application to the lower back only; one subject had a total patch detachment and was almost exclusively responsible the overall decrease in patch area still stuck after the three consecutive tests, at $t = 3.5$ h. Thus, a possible explanation for the highly significant effect of the whirl bath on the patches applied to the lower back was most probably related to a technical feature that had not been anticipated during the design of the study. The "whirl" was generated by injecting air through nozzles inserted into the tub walls. The nozzle was directed on the lower back of the subject. As a consequence, the jet in the tub was oriented on the patch applied on the lower back of the subject that might explain the complete patch detachment at this site. None of the other patches applied to arm or thigh was detached, arguing for the direct effect of the air jet in the whirl bath rather than an effect on the patch.

Maximal and mean forces of removal significantly decreased after extreme conditions, for all application sites. The difference between no change in patch area still stuck and forces of removal could be explained by the fact that the measurement of forces removal quantified a process, i.e. the loss of adhesiveness of the patch that preceded the diminution of the patch area stuck. Here again, the mean forces are higher in the thigh group confirming that the thigh is the best application site of Testopatch®.

No adverse effects and no clinically relevant skin reaction were noted using Testopatch®.

In the present study, and to fulfill the recommendations of the ethical committee, the exogenous testosterone exposure was limited by the short duration of patch application. As previously demonstrated in pharmacokinetic studies, the first 2 h of Testopatch® application did not change the physiological concentrations of testosterone (Raynaud et al., 2008a). For this reason, individual drug concentrations were not assessed.

In summary, the present study showed that Testopatch® was safe and presented good adhesiveness properties allowing its use without specific restrictions, in extreme conditions of physical activities.

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