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Dermal tolerance of two ethanol-based skin antiseptics and their auxiliary agents

Summary

Background: Skin antiseptics are frequently used in healthcare settings for prevention of surgical site infections, but few data exist on their dermal tolerance. Aim of the study was therefore to determine the dermal tolerance of a clear and colored skin antiseptic based on 85 % (w/w) ethanol.
Method: Forearms of 44 subjects were treated with 20 µl skin antiseptic per test area and left for 23 hours semi-occlusive three times. Water, 4 % SDS and a reference antiseptic were used as controls. Treatment sites were assessed visually. The auxiliary agent mixture was occlusively applied nine times over 3 weeks to the back of 213 subjects and 2 weeks later once to a virgin site on the back. Sites were graded for skin reactions using a standardized scale.
Results: The mean tolerability score was lower with the clear (0.79 ± 0.97) and colored antiseptic (0.50 ± 0.58) than the negative control (0.92 ± 1.39) indicating a better tolerance, and was similar to the reference antiseptic (0.59 ± 0.44). The auxiliary agent mixture did not lead to any skin reaction at any time. Tolerability of two ethanol-based skin antiseptics and the auxiliary agents of the colored formulation was good.
Conclusion: When used as intended, no clinically relevant skin irritation should be expected.
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Introduction

The prevention of surgical site infections is one of the major goals in infection control [1]. One standard procedure which is practiced worldwide is the application of a skin antiseptic prior to incision in order to reduce the resident bacterial flora to a minimum. Many preparations for skin antisepsis are based on alcohol such as ethanol, isopropanol or n-propanol [2, 3]. These alcohols have a broad spectrum of antimicrobial activity and are also commonly used in hand disinfection (4). They are also known to be well tolerated by human skin [5].

According to the tentative final monograph for healthcare antiseptic products by the Food and Drug Administration (FDA), ethanol is considered to be safe and effective for skin antisepsis in a concentration of 60 % – 95 % [6]. Other studies on hand disinfectants confirm that commonly used preparations based on 80 % [7], 85 % [8] or 95 % ethanol [7] are well tolerated on healthy skin, even among subjects with an atopic predisposition [7].

Two new skin antiseptics based on 85 % ethanol were recently described [9]. Their major advantage is that the application time on skin with many sebaceous glands (e.g. forehead) is only 2.5 minutes [9] in contrast to most other alcohol-based skin antiseptics, which currently require a 10 minute application time on the same type of skin [2]. Skin antiseptics which require a shorter application time to reveal an equivalent efficacy may have theoretically, due to their composition, a higher dermal irritation potential. Despite all published data on the dermal tolerance of ethanol or ethanol-based antiseptics, it was scientifically essential to determine

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the local tolerance of the two new skin antiseptics and of the mixture of auxiliary agents of the colored skin antiseptic. We have therefore investigated the dermal tolerance of two ethanol-based skin antiseptics in a repetitive semi-occlusive patch test and the potential for skin irritation and sensitization of the auxiliary agents of the colored skin antiseptic in a re-peated insult patch test (RIPT).

Methods

Repetitive semi-occlusive patch test with skin antiseptics

Study design

A mono-centric, prospective, double-blind, controlled (positive and negative control), randomized, clinical trial was performed. It was a repetitive semi-occlusive patch test. The study was conducted in accordance with the ethical principles that have their origins in the current version of the Declaration of Helsinki (52nd WMA General Assembly, Edinburgh, Scotland, October 2000). Approval of the ethics committee of the medical chamber Schleswig-Holstein was granted (07.04.2004, and two amendments on 05.05.2004 and 30.06.2004).

Study preparations

The following preparations were used: skin antiseptic A (trade name: Cutasept med F; clear skin antiseptic), based on 85 % (w/w) ethanol, and the colored version as skin antiseptic B, also based on 85 % (w/w) ethanol (trade name: Cutasept med G). Cutasept F based on 70 % (w/w) isopropanol was used as a reference skin antiseptic. The experiments were controlled with demineralized water (negative control) and 4 % sodium dodecyl sulphate (SDS; positive control). Both skin antiseptics were manufactured by Bode Chemie GmbH, Hamburg, Germany. The test preparations and controls were randomly assigned a letter (blinding of the test formulations).

Selection of study population

A total of 44 subjects were recruited. Subjects were included if they

– Were Caucasian men or women of skin type I to IV according to Fitzpatrick [10]
– Were between 18 and 65 years of age
– Signed written informed consent
– Had a negative urine pregnancy test (female panelists of child bearing potential).

Subjects were excluded if they

– Were pregnant or during lactation
– Had active skin diseases, moles etc.
– Had severe illness on account
– Had psychiatric conditions that might limit the participation
– Took drugs interfering with the immune system (e.g. antiphlogistics, corticosteroids, immunosuppressants or antihistamines)
– Had topical therapy in the test region in the last two weeks
– Had recent intensive UV-light exposure (less than two weeks)
– A known allergy to the ingredients of the test products
– Had a history of drug or alcohol addiction in the past three years
– Had an infectious disease (e.g. AIDS or hepatitis)
– Were insulin-dependent diabetic
– Were known to have poor compliance.

Test procedure

Test areas were marked on both forearms. 20 µl of the coded test material (product or controls) were applied on day 1, day 2 and day 3 to one of the marked test areas according to the randomization list. The test material was left under semi-occlusive conditions for 3 × 23 h (Trumed patches, Trumed Technologies Inc., Burnsville, USA).

Assessment of tolerability

All evaluations were done by the same investigator. Visual assessments were performed before the application on day 1, before each application on days 2, 3 and 4 (15 minutes to 2 hours after patch removal), as well as 48 ± 2 hours after patch removal (day 5) and 72 ± 4 hours after patch removal (day 6).

The following scale was used:

0 No apparent cutaneous involvement
0.5 Faint, diffuse erythema (greater than 0, but less than 1)
1 Definite, moderate to severe erythema but skin intact, without papules
2 Severe erythema (possibly moderate edema) may have a few papules, deep fissures, or other defects of skin surface
3 Very severe erythema, generalized papules or vesicles, and/or other defects of the skin surface extending beyond test site
4 Very severe erythema with edema extending beyond test site and vesicles or eschar formations

In case of a score ≥ 2 on day 2 and 3, no further product was applied. Skin tolerability was expressed as the mean tolerability score over days 4, 5 and 6.

Statistics

For statistical analysis of tolerability data, the visual assessment sum score on study days 4, 5 and 6 was used. Data is presented descriptively as mean ± standard deviation.

Investigation of non-inferiority of test products to reference was planned in the protocol, if clinically relevant intolerance reactions were observed during the study (average sum score > 0.9). The number of premature product discontinuations was planned to be compared using McNemar´s Test.

Analysis is based on the ITT population (all panelists with at least one dose of study medication and at least one post-baseline visual assessment).

Repeated insult patch test with additional auxiliary agents of colored skin antiseptic

Test design

Subjects between the ages of 20 and 70 were recruited. No individual was used if they had a history of acute or chronic dermatological, medical and/or physical conditions which could interfere with dermal scoring, or treatment with sympathomimetics, antihistamines, non-steroidal anti-inflammatory agents, and/or corticosteroids in the week before the study began.

In order to remove sebum, dead skin cells or any traces of cosmetic or toiletry products, the test area was gently wiped using one or two wipes of alcohol-soaked cotton (70 % isopropyl alcohol). This was done only prior to the first induction patch application and the challenge patch application, since the subjects were instructed not to use any products on the test sites during the study. The test material (0.2 ml) was allowed to volatilize and was applied under an occlusive patch (occlusive strip with Flexcon, TruMed Technologies Inc., Burnsville, Minnesota, USA) to the upper back between the scapulae. The test material was allowed to remain in direct skin contact for 24 h.

Test formulation

The colored skin antiseptic contains, in addition to the clear skin antiseptic, two dyes (E 104 and E 131) and a thickener (povidone pyrrolidone), resulting in a total concentration of all three agents of 0.0391416 %. The three agents were prepared as a mixture with the appropriate concentration in sterile water. The test formulation was manufactured by Bode Chemie GmbH, Hamburg, Germany.

Induction period

Patches were applied to the same site on Mondays, Wednesdays and Fridays for three weeks (nine applications). Patches were removed by the subjects on Tuesdays, Thursdays and Saturdays. The sites were graded by a person trained to score for degrees of erythema and edema under the supervision of a dermatologist. Grading was done immediately prior to the next product application, which was either 24 h after Tuesday's and Thursday's patch removal or 48 h after Saturday's patch removal.

Challenge period

After two weeks rest, the challenge patches were applied to previously untreated test sites on the back. After 24 h, the test patches were removed by a technician. The test sites were evaluated for dermal reactions immediately after removal of the patches as well as 48 and 72 h later.

The sites were graded according to the following scoring system:

0 No visible skin reaction
± Barely perceptible erythema (minimal)
1+ Mild erythema (diffuse)
2+ Well defined erythema
3+ Erythema and edema
4+ Erythema and edema with vesiculation

Results

Repetitive semi-occlusive patch test with skin antiseptics

One of 44 subjects dropped out on study day 1 due to reasons unrelated to the test preparations. Among the remaining 43 subjects (ITT population), 22 were female and 21 male. The mean age was 44.4 ± 12.8 years. Most volunteers were of skin type II (41.9 %), followed by skin type III (37.2), V (14.0) and I (7.0 %).

The overall mean tolerability was 0.79 ± 0.97 with skin antiseptic A, and 0.50 ± 0.58 with skin antiseptic B, which was lower to the mean tolerability of the negative control (0.92 ± 1.39). The reference skin antiseptic was found to have a mean score of 0.59 ± 0.44. The positive control with 4 % SDS revealed a significantly higher value (3.70 ± 2.72). For both test preparations, the mean tolerability score proved to be well below 0.9, indicating a good to very good tolerability. Therefore no further analysis of non-inferiority was performed.

A total of 6 premature product discontinuations were observed, all on study day 3. Five times the discontinuation applied to a test area treated with the positive control, once to a test area with demineralized water.

Since there were no discontinuations on areas treated with the test products, no statistical comparison could be performed meaningfully.

Repeated insult patch test with additional auxiliary agents in colored skin antiseptic

224 subjects were enrolled, 213 of them finished the study. Eleven discontinued for reasons unrelated to the test preparation. Thirty-eight of the 213 subjects were male (17.8%), 175 were female (82.2%). The mean age was 43.9 ± 12.1 years. None of the 213 subjects had any reaction at any time after each of the 9 induction applications. All 213 subjects had no visible skin reaction 24, 48 or 72 h after the challenge application.

Discussion

Although little is known on the incidence and severity of skin irritation among patients who have been treated with alcohol-based skin antiseptics, it is essential to have evidence that a skin antiseptic is well tolerated when used as intended. We provide evidence that both ethanol-based skin antiseptics are well tolerated on intact skin when applied repetitively under semi-occlusive test conditions. In addition, the auxiliary agents of the colored skin antiseptic did not show a clinically relevant potential of irritation or sensitization.

The study population of the repetitive semi-occlusive patch test can be considered to be a susceptible one. Treatment with 4 % SLS induced a remarkable degree of skin irritation (3.70 ± 2.72) and shows that the current study population can be classified as susceptible in the context of other study data [7]. Alcohols are considered to be the most suitable type of active agents in skin antisepsis because their antimicrobial efficacy on the resident skin flora is broad and fast in comparison to other active agents, such as povidone iodine [11] or chlorhexidine gluconate [4, 12]. In addition, alcohols are in general well tolerated by human skin [5, 13]. Even when the skin is pre-irritated, alcohols usually do not enhance the irritation [5, 14].

It is, however, important to allow the alcohol to completely evaporate. Few cases of burn after use of alcohol-based skin antiseptics have been reported when the healthcare worker began to use the diathermy before complete evaporation of the alcohol [15]. That is why the safe use of alcohol-based skin antiseptics includes the patience of the healthcare workers to allow the alcohol to evaporate [16]. Based on this knowledge, it becomes even more important to identify the shortest possible application time which is equally effective to the commonly used application time [17, 18]. For our two test preparations, a 2.5 min application was found to be equally effective to the formerly accepted 10 min application time on skin with many sebaceous glands (9). This important step towards evidence-based infection control will allow to use the limited resources in hospitals more efficiently as previously shown for surgical hand disinfection.

Azo-dyes like e. g. brilliant black (E 151) or orange yellow S (E 110) are the most important and largest group within dyestuffs. They are synthesized by conversion of aromatic amines with differently substituted aromatic substances in the presence of sodium nitrite and hydrochloric acid. Under certain conditions which are normally not found on intact skin, the azo-group may be reductively cleaved. In this case the starting compound, an aromatic amine like aniline derivatives, may be released which may have, depending on the specific type of dye, a carcinogenic potential. This has, however, so far never been described from commonly used skin antiseptics containing azo-dyes. Neverthe-

less, non-azo-dyes have become favorable for application on human skin. The two dyes in the colored skin antiseptic are authorized in Appendix I of Council Directive 94/36/EC and are permitted for use in medicinal products. They did not reveal a clinically relevant potential for irritation or sensitization and should therefore be safe for use on intact human skin. Only with E 131 rare anaphylactic reactions to the dye have been reported when used intraoperatively, e.g. for lymphatic mapping [19]. A cross-reactivity to E 131 has also been reported in one patient with a type I allergy to isosulfan blue [20]. These cases are apparently very rare and have to date not been described after application of the dye to intact skin.

Conclusions

We were able to show that two commercially available ethanol-based skin antiseptics were well tolerated by subjects in a repetitive semi-occlusive patch test in a maximized test design. It can therefore be expected that the dermal tolerance of both skin antiseptics will be very good under clinical conditions. Neither the thickening agent nor the dyes used in the colored skin antiseptic are likely to have a clinically relevant potential for sensitization.

Conflict of Interest

The corresponding author is employee of Bode Chemie GmbH, Hamburg, Germany.

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