A double-blind, randomized clinical study to determine the efficacy of benzocaine 10% on histamine-induced pruritus and UVB-light induced slight sunburn pain

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Abstract

Introduction: This study aims to explore the efficacy of the topical application of 10% benzocaine for treating pruritus and pain as compared to vehicle ointment. Methods: Twenty male subjects were treated in a randomized double-blind fashion with the investigational medicinal product (IMPD) and vehicle. Immediately after the injection of 100 μg histamine on both arms, subjects received topical treatment and pruritus was subsequently assessed with visual analogue scale (VASpruritus) and Eppendorfer questionnaire. Ultraviolet B radiation (UVB) was administered on the back to induce slight sunburn. Twelve hours after UVB application again the IMPD was applied on the right or left upper back and vehicle on the other side and pain related to sunburn was measured with VASpain and pressure algometry. Results: A trend towards better reduction of pruritus was shown for benzocaine in VASpruritus. For the VASpain significant differences in group comparison (p = 0.02) were observed. Algometer measurements showed onset of pain reduction in the verum group after 20 min whereas in the vehicle-treated area pain relief occurred only after 60 min after application. Conclusions: The topically administered ointment containing 10% benzocaine was found superior over vehicle for treating pain, but not pruritus.

Keywords

Benzocaine, local anaesthetic, methaemoglobin, pain, pruritus,

Introduction

Local anaesthetics (LA) are often applied to relieve pain or itching sensations caused by various conditions. However, there is a lack of scientific formally correct clinical studies to confirm vast knowledge that has grown in less formal ways evaluating the efficacy of these drugs (1). The procaine derivate benzocaine (4-aminobenzoic acid ethyl ester; ethyl p-aminobenzoate) is a member of the pharmacological class of LA. The cutaneous analgesic action of topical anaesthetics targets free nerve endings by preventing the initiation and transmission of nerve impulses (2). This mechanism is achieved by limiting sodium ion permeability by binding to a specific receptor site within the pore of the voltage-gated sodium channels and blocking ion movement through this pore. Benzocaine, perhaps because of its small size and because of its lack of a tertiary amine component, has been proposed to have separate binding sites from that of traditional LA (3). The medicinal product 'Anaestherit-10%' contains 10 g of the LA benzocaine in 100 g ointment which is approved for treating pain caused by burn wounds and sunburn.

Benzocaine is frequently used for the local anaesthesia in the mouth to relieve pain caused by toothache, needle injection or for topical anaesthesia of mucous membranes before endoscopic procedures. Several studies revealed the superior efficacy and fast onset of action of benzocaine as anaesthetic agent to mucous membranes when compared to e.g. lidocaine or to placebo (4–12). Some other studies describe no significant differences in efficacy between benzocaine and the comparator topical anaesthetic administered on mucous membranes, even though pain reduction has been observed (13–15). Other older studies investigating topical application of benzocaine on the skin were not conducted double-blind or vehicle-controlled, so they cannot prove efficacy. (16–18).

The tolerance of benzocaine is well-recognized based on a long application history. Only weak side effects like minor headaches in individual people could be recognized. Methaemoglobinemia induced by benzocaine was occasionally reported as a possible side effect when used as a topical oropharyngeal anaesthetic (19) and rarely after dermal application (20,21).

Due to the lack of randomized, controlled studies, the present study set out to compare the activity of Anaestherit-10% in a double-blind fashion to vehicle. For period one of the study a histamine (pruritus) model and for period two an ultraviolet B radiation (UVB) (sunburn) model has been used. Pruritus is an unpleasant sensory perception of the skin associated with the desire to scratch. Itch can be defined as a separate, pain-independent sensation with its own mediators, spinal neurons and cortical areas (22). Since many decades histamine has been used as the pruritic stimulus in clinical studies (23–25). The onset of pruritus in histamine models is reported to be between 1 and 5 min after histamine application (26,27). The histamine model is
considered to be superior to the recently published administration of cowhage (Mucuna pruriens) spicules on the superficial skin e.g. as a model of itch due to insect bites (26). Pain related to UVB-induced sunburn is an established, simple, acute pain model (28,29). The measurement of pain under standardized conditions using an algometer was described earlier (30,31).

Methods

Ethics

This study is registered with EudraCT, number 2012 - 00283527. The study protocol, the informed consent form and the subject information sheet have been approved by the Ethics Committee of Medical University of Vienna, Austria. The study was carried out in accordance with the Austrian drug law (AMG) and the rules of Good Clinical Practice (GCP) as laid down in the European guideline on Good clinical practices (CPMP/ICH/135/95) in its currently valid version. The clinical work was conducted in accordance with the ‘Declaration of Helsinki’ (Seoul, Republic of Korea, 2008).

Study drugs

For the present study one batch of the vehicle ointment containing white petrolatum, bis-diglyceroyl polyacyladipate-2, polysorbate 80, medium chain triglycerides and myristyl myristate and one batch of the investigational medicinal product (IMP) Anaestherit 10%, containing additionally benzocaine, white petrolatum, bis-diglyceroyl polyacyladipate-2, polysorbate 80, medium chain triglycerides and myristyl myristate, were used. Both were provided by Dr. Ritsert Pharma GmbH & Co KG, Eberbach, Germany. In order to induce pruritus, approximately 100 μg of histamine (Cepelone®, 0.5 mg/0.5 ml solution for injection, Meda Pharmaceuticals, Wien, Austria) was injected intracutaneously on both fore arms.

UV irradiation

The UVB irradiation source used was a UVB system (UV 109 B; Waldmann, Villingen-Schwenningen, Germany; emission spectrum 280–360 nm, peak 370 nm). The lamp was housed in a carton tube with one round aperture of 2 cm diameter in the side. UV radiation was given by applying the lamp directly to the skin. To define the minimal erythema dose (MED), skin areas with 2 cm diameter were irradiated with the following defined doses of approximately 45, 80, 105, 140, 170, 195 and 230 ml/cm² corresponding to the irradiation time of approximately 4, 7, 9, 12, 15, 17 and 20 seconds. The UVB-irradiated skin areas were rated with the clinical erythema assessment score consisting on a 4-point categorical scale (0: None; 1: mild; 2: moderate; 3: severe).

Experimental design

The study was performed as double-blind randomized clinical trial with two periods. The primary efficacy variables as defined in the protocol for the pruritus model (period 1) was the difference of mean VASpruritus between the administered sites, on which benzocaine 10% or vehicle was applied and for the pain model (period 2) the difference of mean pain measurement between the administered sites using the Algometer FDX (painalgom). Secondary endpoints included Eppendorf itch questionnaire (EIQ) and VASPain.

Healthy volunteers were recruited from the database of the Department of Pharmacology. Subjects with history of psoriasis, neurodermatitis or eczema were not eligible for the study. Totally 21 healthy male Caucasian subjects aged ≥ 18 years with intact skin (i.e. no skin breaks or other skin disorders at the test areas) were screened for study participation. Twenty subjects were included in the study. They had a mean age ± standard deviation of 25.2 ± 3.0 years (range, 20–30 years), mean body weight of 76.0 ± 11.2 kg (range, 57.8–97.8 kg), and mean height of 183 ± 7 cm (range, 172–195 cm). For period 1, areas of 25 cm² were marked on each forearm; in the middle of these areas 100 μg of histamine were injected intracutaneously at the same time for both arms. Immediately after histamine injection, 1 g of ointment containing 10% benzocaine or 1 g vehicle ointment was applied on the respective forearm simultaneously in a randomized double-blind fashion. Each subject had to rate the intensity of pruritus using VASPpruritus at 1, 3, 6, 9, 12 and 30 min after application of the ointment separately for both arms. The EIQ (1 b) was performed immediately after VAS-rating separately for right and left forearm. The time-points have been chosen based on previously reported studies according to the expected peak efficacy of benzocaine and histamine (27,32). At the end of the same study day, the MED was defined by UVB irradiation of selected skin areas on the right with a diameter of 2 cm each. The readout of UVB-light induced sunburn was carried out 24 h after application of UVB. Thereafter a wash-out phase of 7–14 days in order to avoid carry over effects followed.

On the evening before the study day of period 2, subjects were confined at the study ward. They received UVB at their individual MED on the right and left upper back (2 cm diameter). On the following morning, 12 h after induction of sunburn, a baseline VASPain as well as the measurement of painalgom was performed. Immediately after pain-rating, simultaneous application of either 1 g investigational medication on the one site and vehicle on the other site was performed in a randomized and blinded way. Thereafter spontaneous pain determined by VASPain as well as the pressure induced pain was assessed at 10, 20, 30 min, 1 hour and 6h after application of the ointments in order to evaluate both pain components of sunburn, superficial spontaneous pain as well as deep-seated induced pain.

The occurrence of adverse events was continuously assessed and recorded from day 1 until final examination. For safety assessment, vital sign and adverse event recording as well as blood draws for standard laboratory tests including chemistry, haematology and methaemoglobin measurements were performed on screening, after period 1 and on the final examination visit.

Evaluation of efficacy

Visual analogue scale

The rating for pruritus and pain has been performed using the validated one-dimensional measure VASPpruritus and VASPain respectively (27,33). The subjects were instructed to rate the spontaneous pain on the VASPain scale. Far left end indicates “no pain” (corresponding to score 0) and the far right end indicates “worst pain ever” (corresponding to score 10). Volunteers were advised to rate the pruritus on a Visual analogue scale (VAS) which was documented as VASPpruritus. Far left end indicates “no pruritus” (corresponding to score 0) and the far right end indicates “worst pruritus ever” (corresponding to score 10).

Eppendorf itch questionnaire

The subjects had to complete the EIQ part 1 b in a modified version containing 24 items describing sensory qualities. They had to rate each item on a “0” to “4” point scale, “0” meaning “not appropriate” and “4” “absolutely appropriate”. The original questionnaire (“Eppendorf Juckreiz-Fragebogen”) includes 80 questions (34), whereas the shortened questionnaire used in the present study includes 24 items previously generated by Kosteletzky et al. (35).
Pressure algometry

A hand-held pressure algometer (Wagner Force Ten™ FDX 50 Compact Digital Force Gage, Wagner Instruments, Greenwich, CT) with a 1 cm² flat circular rubber tip was used to quantify deep-seated pressure pain in kilograms of force (kgf). Subjects were instructed to tell the investigator as soon as they experienced pain.

Values outside mean value ± three sigma were predefined as outliers. Regarding algometer measurements, mean value ± three sigma were 6.85 ± 8.72, therefore, values above 15.57 were excluded from all analysis. This resulted in exclusion of the value of algometer measurement at 1 h after treatment with investigational product from subject 18 and values at baseline and at time points 20 min, 1 h and 6 h after treatment with vehicle as well as the 6 h value after treatment with vehicle for subject one.

Determination of sample size

The sample size calculation of this study was based on the results of the controlled and randomized study published from Czepa et al. (30). The primary power calculation was based on the sunburn pain model. Therefore, the intensity of pain as estimated applied force in Newton (1 kgf to 10 N) needed to induce pain was used. A change in applied Newton of more than 10% was considered clinically relevant. Taking into account these assumptions the sample size was determined as follows: An assumed difference in experience of pain of 12 Newton (basic value 43 ± 17 Newton determined in the study named above) resulted in a sample size of 18 subjects per group. We conducted the Power Analysis with \( \beta = 20\% (0.80) \) and \( \alpha = 0.05; \) according to a expected dropout rate of 5 % the maximum recruiting number of subjects was 21 subjects which means a safety of 1 subject.

Statistical analysis

AUC for VAS (for pruritus and pain) and algometer measurements were calculated with Microsoft Excel for Windows (version 2003, Microsoft, New York, NY).

Statistical analysis and descriptive statistics was performed by the STATISTICA software package for Windows (version 5, StatSoft Inc., Tulsa, OK). According to the Shapiro–Wilk test, values for pruritus and pain measurements of the IMPD and vehicle group were not normally distributed. Therefore Wilcoxon matched pairs test was used for comparisons of IMPD and vehicle. The Friedman test was used to test for changes between the single time points of the observed time period.

Results

Twenty subjects who received 10% benzocaine and vehicle ointment after intracutaneously histamine challenge were analysed for efficacy and safety with regard to pruritus. One subject did not get sufficient sunburn at the investigated UVB exposure and dropped out from the study before period 2, therefore 19 subjects were included in the efficacy analysis for UVB induced pain. The applied UVB dose, i.e. the individually assessed MED, corresponded in all but one subject to a clinical erythema assessment score of moderate redness of the skin. The individual demographic data for each subject are listed in Supplementary Table 1.

The results of the \( VAS_{pruritus}, VAS_{pain} \) and \( pain_{algom} \) are shown in Figures 1–3.

No significant differences for \( VAS_{pruritus} \) measurements were calculated for IMPD and vehicle for the single values (Wilcoxon matched pairs test \( p<0.437 \)) and the time course (Friedman test \( p<0.059 \)). The mean area under the \( VAS_{pruritus} \) time-curve ± standard error of the mean \( (AUC \pm SE/cm*min) \) was 49.70 ± 10.69 for the IMPD and 56.00 ± 11.41 for the vehicle treatment. The mean results for \( VAS_{pruritus} \) are depicted in Figure 1 and the EIQ values are presented in Supplementary Table 1.

For \( VAS_{pain} \) (Figure 2), statistically significant differences were observed between the groups (Wilcoxon matched pairs test \( p=0.013 \)) and for time course (Friedman \( p=0.012 \)). \( VAS_{pain} \) AUC values of both groups showed no statistically significant difference in the Wilcoxon matched pairs test comparison. The mean \( VAS_{pain} \) AUC ± SE/cm*min values were 43.33 ± 5.93 for the benzocaine treatment and 71.89 ± 16.60 for vehicle. Measurements of pain using the algometer FDX are depicted in Figure 3. The mean \( pain_{algom} \) AUC ± SE/kgf*min was 2350.72 ± 136.79 for the IMPD and 2204.59 ± 114.25 for vehicle. Comparisons between two groups including all time points resulted in no statistically significant difference in perception of pressure-pain. However, statistically significant differences were derived for the time course (Friedman \( p=0.026 \)). The descriptive
The present study was planned as double-blind, vehicle controlled clinical trial evaluating the efficacy of the benzocaine containing ointment for treating pruritus and pain in two distinguished models. In the present study, the clinical efficacy of benzocaine as pain relieving active ingredient was confirmed. Nevertheless, it could be demonstrated that this pain intensification of spontaneous pain. It was therefore difficult to reveal significant changes in pain when the IMPD and the vehicle were compared. Furthermore, a high inter-individual variability has been observed. Nevertheless, there was a statistically significant difference in spontaneous pain underlying the superior efficacy in pain reduction of benzocaine as compared to vehicle ointment. Effect was observed through all time-points until 360 min after application (Figure 2), however, maximum difference between the two groups has been seen between 10 and 20 min after application of the treatment, pointing out the time frame of maximum effect of benzocaine. During the subsequent time course the difference between the two groups becomes lower indicating that repeated administrations might become necessary for clinical treatment.

Additionally to the VAS rating as a subjective measure of spontaneous pain perception, the algometer induced pain has been used for measurement of anti-nociceptive treatment effects. While the onset of pain reduction occurred in the benzocaine group after 20 min, the vehicle treated area showed pain relief only after 60 min after application. After the first measurement of pain both treated sides of the subjects showed pain intensification. This might be due to the physiological development of sunburn up to 24 h after induction. An additional point to consider is the physical irritation of the sunburn area by the algometer, possibly leading to higher perception of pain at subsequent measurements. Nevertheless, it could be demonstrated that this pain intensification was less pronounced for the sunburn area treated with benzocaine, indicating prevention from pain aggravation due to physical irritation by the benzocaine containing ointment.
In the US benzocaine has been an OTC since 1926 and has been found to be one of the safest topical anaesthetics available (11,41). In contrast to other LAs benzocaine is poorly water soluble, therefore systemic absorption via the skin is low and blood levels might be both sub-analgesic and insufficient to cause systemic adverse reactions (42).

In the present study no serious adverse events were observed. Flush and feeling of heat and sweat were attributed to histamine activity and are most probably not allergic type reactions or reactions due to sensitization of the subjects to benzocaine. In addition two cases of slight methemoglobinemia did occur in the present study. Both subjects had high baseline values (1.0% and 0.9% respectively) and a very low increase in methaemoglobin value (0.1%), thus the observation was not considered clinically relevant. It is generally reported that clinical relevant symptoms due to methaemoglobinemia occur at levels beginning from methaemoglobin levels of 10 - 20% and in rare cases led to cyanosis (43). In most cases the cyanosis is benign, but untreated, especially when Met-HB levels are over 30% can lead to major cardiopulmonary compromise, neurologic sequel, and even death (44). A study evaluating the incidence of methaemoglobinemia associated with the application of 20% benzocaine spray during 28 478 episodes of transesophageal echocardiography identified only 19 cases with clinical presentation of methaemoglobinemia, assuming that the incidence of benzocaine-induced methaemoglobinemia is 1 case per 1499 (0.067%; 95% confidence interval, 0.040–0.100%) (45). Considering the available literature, it seems that methaemoglobinemia is mostly elicited in situations where systemic absorption might be higher compared to intact normal skin (20,21). Cases of methemoglobinemia involving self-application by patients are rare and typically involve significant overdoses of the drug (46). It can be concluded that the application of the ointment containing benzocaine in this study did not result in significant increase of methaemoglobin values and was far from producing clinical relevant methaemoglobinemia.

The main limitation of the study is the small sample size which was large enough for the detection of significant differences between IMPD and vehicle for the pain but not the pruritus model. Moreover, there are both itch- and pain-specific nerve fibers on the skin. There is evidence that different nerve fibres sense different kinds of itch (47,48). Furthermore, only single dose administration was investigated. This study provides valuable information for further studies investigating benzocaine’s effect on pruritus. Strengths of the study include experimental design features. In contrast to previous studies investigating benzocaine formulations for dermal application, this study was conducted double-blind and vehicle-controlled. Carry over effects were avoided with a design foreseeing one separate study day for each model and with an ample wash out period in between the study days. Study end points were investigated with independent, widely used and evaluated models and assessments. The present trial is the first proving clinical efficacy of a 10% benzocaine containing ointment.

Conclusions

We conclude that the ointment containing 10% benzocaine is well tolerated and safe. For the pain model statistically significant differences in pain reduction for the benzocaine treatment was shown.

Declaration of interest

The Medical University of Vienna received financial compensation for conducting the study, MB, RS, TS and MZ did not personally receive payment from the sponsor or FORIM. The FORIM GmbH received financial compensation for the independent preparation, planning and evaluation of the study. ILZ and KN did not personally receive payment from the sponsor.

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