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Anti-inflammatory activity of hamamelis distillate applied topically to the skin

Influence of vehicle and dose

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Summary. The anti-inflammatory activity of hamamelis distillate has been evaluated with respect to drug concentration (0.64 mg/2.56 mg hamamelis ketone/100 g) and the effect of the vehicle (O/W emulsion with/without phosphatidylcholine (PC) in an experimental study. The effects were compared with those of chamomile cream, hydrocortisone 1% cream and 4 base preparations. Erythema was induced by UV irradiation and cellophane tape stripping of the horny layer in 24 healthy subjects per test. Skin blanching was quantified by visual scoring and chromametry. Drug effects were compared with one another and with an untreated control area, as well as with any action due to the vehicle.

UV-induced erythema at 24 h was suppressed by low dose hamamelis PC-cream and hydrocortisone cream. Hydrocortisone appeared superior to both hamamelis vehicles, hamamelis cream (without PC) and chamomile cream. The latter preparation was also less potent than hamamelis PC-cream. Erythema 4 to 8 h after the stripping of the horny layer was suppressed by hydrocortisone ($P \leq 0.05$). Inflammation was also less pronounced following low dose hamamelis PC-cream and chamomile cream. Hamamelis PC-cream, however, appeared less potent than hydrocortisone. In general, visual scoring was more discriminatory than chromametry.

The results have demonstrated an anti-inflammatory activity of hamamelis distillate in a PC-containing vehicle. A fourfold increase of drug concentration, however, did not produce an increase in activity.

Key words: Hamamelis, Chamomile, Hydrocortisone; anti-inflammatory activity, vehicle effects, UV-erythema test, cellophane tape stripping, phosphatidyl choline

Despite the unquestionable efficacy, the use of topical glucocorticoids today is limited by adverse effects [1, 2]. These include numerous local and systemic reactions, varying from mild to life-threatening. Skin atrophy and suppression of the hypothalamic-pituitary-adrenal axis are their most feared actions, and much effort is taken to reduce them. Besides optimisation of the drug molecule [3] and the therapeutic regimens [4], herbal drugs, e.g. chamomile extracts and hamamelis distillate [5–7], have been tried to reduce the need for glucocorticoids. The FDA regards hamamelis distillate as safe and effective [8]. Anti-inflammatory activity is considered to result from reduced skin blood flow [9] due to the vasoconstrictor activity of the hamamelis tannin. Beyond that, a diminution in histamine release by flavones or radical capture by flavone glycosides have been discussed [10].

There is, however, a lack of studies conforming to present standards in clinical pharmacology demonstrating the efficacy and safety of herbal dermatologicals. This holds true both with respect to experimental dermatoses induced in healthy volunteers and to efficacy in various inflammatory skin diseases, e.g. atopic dermatitis. In particular, the effects of herbal and nonherbal drugs have only rarely been compared [5, 11, 12]. This also applies to studies of the influence of the vehicle and, even more strongly, to examinations of the effect of the drug concentration, all of which are important.

Besides increased drug concentration, liposomal encapsulation or the addition of phospholipids may enhance the activity of topical dermatics. Due to their mild actions, this would be particularly desirable for herbal dermatics. An improved pharmacological effect due to liposome encapsulation has been demonstrated for many drugs, e.g. tetracaine [13], α-interferon [14], and T4-endonuclease [15]. In the case of liposomal betamethasone dipropionate, a clinical trial suggested increased activity in atopic dermatitis as compared to an optimised gel preparation [16]. Jacobs et al. demonstrated an increased vasoconstrictor response after application of phospholipid liposomes in addition to glucocorticoid cream preparations, and suggested that phospholipids, such as phosphatidylcholine (PC), improved local availability [17].

Recently, a phospholipid containing hamamelis preparation has been introduced, replacing the corresponding conventional O/W cream. In the present study in healthy volunteers, the anti-inflammatory activity of three *Hamamelis virginiana* preparations (standard and high dose

in a PC-containing vehicle, and a standard dose in a cream without added PC) have been compared with cream preparations with hydrocortisone and chamomile extract, as well as four base preparations.

Materials and methods

Design

These were two randomised, double-blind studies. Inflammation was induced by UV irradiation and cellophane tape stripping. After approval by the local ethical committee, 48 healthy subjects (17 m, 31 f; aged 22–40 y; no hyper-sensitivity to hamamelis, chamomile, glucocorticoids or ingredients of topical dermatics/cosmetics; no intense sun tanning of the test area; no glucocorticoids systemically or topically on large surface areas during 6 weeks, or any drug treatment of the test area for at least 7 days prior to the study; no pregnancy/lactation) participated in the study after giving written, informed consent. The test area was the skin of the back below the shoulder blades. Blood samples for blood count, serum creatinine, SGOT, SGPT and γ-GT were taken before and after the study.

Test preparations

Five cream preparations containing active ingredients were tested. They comprised two oil-in-water (O/W) emulsions with *Hamamelis virginiana* distillate (5.35 g with 0.64 mg hamamelis ketone per 100 g, Hametum®, and 2.56 mg hamamelis ketone/100 g; W. Spitzner, Ettlingen, Germany). The PC-vehicle contained phospholipids ($\geq 85\%$ PC; Phosal®, Nattermann-Phospholipid, Köln, Germany). The lower dose of hamamelis ketone was also applied in the corresponding oil-in-water base without PC addition (Hamamelis cream; W. Spitzner, Ettlingen, Germany). The other active preparations were creams containing chamomile extract (20 mg/g Kamillosan® Creme, Asta Medica, Frankfurt/M., Germany) or 1 % hydrocortisone (Hydrocortison-Wolff 1,0 Creme, Dr. August Wolff, Bielefeld, Germany). In addition, four drug-free base preparations were also tested, which were the vehicles corresponding to both hamamelis creams (PC-vehicle and O/W-vehicle-1; W. Spitzner, Ettlingen, Germany) as well as another O/W emulsion (O/W-vehicle-2) containing shorter-chain ingredients (Dermatop® Basiscreme), and a W/O emulsion (W/O vehicle; Dermatop® Basissalbe; Cassella-Riedel Pharma, Frankfurt/M., Germany). The test preparations were kept in neutral, coded syringes.

UV-erythema test

This experiment was performed in 24 subjects, according to DIN 67.501 and the procedure described by Ljunggren et al. [18]. The radiation source was a UV 800 lamp (Waldmann, Villingen-Schwenningen, Germany) emitting mainly UV_B and only small amounts of UV_A and visible light. The distance to the skin was 50 cm. Individual sensitivity (minimal erythema dose, MED) to UV_B was determined 24 h before the start of the study by a light scale. One MED is the smallest amount of UV_B producing distinct erythema. For testing, 1.5 MED was applied to 10 areas (3 cm × 2 cm). Test sites were defined using a perforated template. After the irradiation, 75 µl of each test preparation was applied to 9 test sites in random order. One area remained untreated and served as control. After 24 and 48 h the effects were rated by a visual score: 0 intense redness, no effect; 1 marked but not maximum erythema; 2 faint residual erythema; and 3 total erythema suppression. In addition, reflected light colour was determined by chromametry (Chromameter CR-200, Minolta, Ahrensburg, Germany; L*a*b*). The changes in skin redness (Δa^*) and total skin colour (ΔE^*) were compared to an untreated area of the back for analysis.

Cellophane tape stripping

In each subject six test sites (2 cm × 3 cm) were prepared by repeated stripping of the skin with adhesive tape (Tesafilm®, Beiersdorf, Hamburg), as described by Wells [19]. Seventy five µl of each test preparation was applied to five test areas in random order, and another remained untreated and served for control. Twelve subjects received the low dose hamamelis cream and the corresponding vehicle as well as chamomile cream (Group 1), and 12 volunteers received hydrocortisone cream, hamamelis PC-creams (low and high dose), the corresponding vehicle and O/W-vehicle-2 (Group 2). Skin colour was determined after 4, 8 and 24 h by chromametry and using a 5-point visual rating scale (0 very intense redness, no discernable blanching in comparison to the untreated stripped skin; 1 intense erythema; 2 moderate erythema; 3 faint residual erythema; and 4 no erythema, skin colour same as intact skin or brighter).

Side effects

The test area was inspected at each visit for adverse effects and the subjects were asked about them, too.

Statistical analysis

In this exploratory study, the sums of the individual score values and mean values of Δa^* and ΔE^* are given. Skin redness following the various test preparations and the control area was compared by the Wilcoxon-Pratt test. (Exact) $P \leq 0.05/0.10$ was considered to indicate a difference/a noteworthy result.

Results

UV-erythema test

UV-irradiation induced marked erythema at 24 h, which had almost completely faded after 48 h. Thus, only the first reading was suitable for the evaluation of drug effects. The effects of the various test preparations on skin redness (sum of the individual visual score values) is shown in Table 1. A noteworthy reduction in erythema compared to the control area was found only after use of the low dose of hamamelis PC-cream and hydrocortisone 1 % cream ($P = 0.0625$). A comparable difference was also observed between the effects of the former preparation and chamomile cream ($P = 0.0625$) which did not suppress UV-induced erythema. The results suggest superiority of hydrocortisone over the PC-vehicle and O/W-vehicle-1 ($P = 0.0156$), and the hamamelis O/W ($P = 0.0762$) and chamomile ($P = 0.0469$) creams.

Changes in redness and total skin colour, as determined by chromametry, did not indicate a significant difference from the control area. There was, however, a noteworthy reduction in Δa^* and ΔE^* following hamamelis creams, hydrocortisone cream and O/W-vehicle-1 as compared to the PC-vehicle treated area (data not shown). A reduction in redness was also observed with the high dose hamamelis PC-cream as compared to the W/O-vehicle ($P < 0.10$).

Table 1. Sums of visual scores in 24 volunteers 24 and 48 h after irradiation with 1.5 MED of UV_B and application of the test preparations. Scoring: 0 intense redness, no effect; 1 marked but not maximum erythema; 2 faint residual erythema; 3 total erythema suppression

Preparation	24 h	48 h
Hamamelis cream	23	39
O/W-vehicle-1	24	40
Standard hamamelis PC-cream	29	42
High-dose hamamelis PC-cream	27	37
PC-vehicle	24	37
Hydrocortisone 1% cream	31	42
Chamomile cream	22	39
O/W-vehicle-2	26	40
W/O-vehicle	28	42
Control area	24	39

Table 2. Sums of visual scores 4, 8 and 24 h after stripping of the horny layer and application of the test preparations. There were 12 volunteers in each part of the test. Scoring: 0 very intense redness, no discernable blanching in comparison to the untreated stripped skin; 1 intense erythema; 2 moderate erythema; 3 faint residual erythema; 4 no erythema, skin colour same as intact skin or brighter

	Group 1			Group 2		
Preparation vs. time (h)	4	8	24	4	8	24
Hamamelis cream	15	18	33			
O/W-vehicle-1	14	16	30			
Standard hamamelis PC-cream	17	17	29	27	28	33
High dose hamamelis PC-cream				28	30	33
PC-vehicle	15	16	32	28	29	34
Hydrocortisone 1% cream				34	34	32
Chamomile cream	17	19	30			
O/W-vehicle-2				29	28	34
Control area	9	14	32	24	24	33

Cellophane tape stripping

The erythematous reaction to the stripping of the horny layer faded rapidly (Table 2). Thus, only the changes in skin redness 4 and 8 h after stripping and drug application were suitable for the analysis of drug effects. Statistical analysis suggested that hydrocortisone 1% cream was superior to the control area at 4 and 8 h. The respective P-values are < 0.01 for the visual score and < 0.05 for Δa^* (7.49/6.57 vs. control 9.43/8.81 at 4/8 h) and ΔE^* (8.92/7.58 vs. control 11.21/10.52). A noteworthy difference to the control was also obtained in the visual scores for hamamelis standard ($P = 0.0937$ at 4 h; Group 1) and high dose PC-cream ($P = 0.0703$ at 8 h), as well as chamomile cream ($P = 0.0625$ at 4 h). Chromametry suggested superiority of the standard hamamelis PC-cream over its vehicle at 4 h (Δa^* 8.68 vs. 9.32 and ΔE^* 9.51 vs. 12.84; $P < 0.1$; Group 2). Hydrocortisone 1% cream appeared superior to the vehicles ($P < 0.1$ in 10 out of 12 tests on visual scores and chromametry). Comparing the effects of the active preparations, hydrocortisone 1% cream appeared superior to hamamelis PC-creams in 9 out of 12 tests according to the visual scores and chromametry data ($P < 0.1$).

Drug and vehicle related side-effects were not observed or reported by the subjects in the UV-erythema test or in the cellophane tape stripping assay.

Discussion

Fearing adverse effects, physicians as well as patients try to avoid glucocorticoid therapy as far as possible. This holds true especially for atopic dermatitis, because its chronic course and frequent relapses require long-term treatment. Thus, possible alternatives to topical glucocorticoids are being sought. Bufexamac is only marginally if at all efficacious [5, 20, 21], and the value of other cyclooxygenase inhibitors in clinical practice is low [22]. Tar preparations and UV light, although active, bear the risk of inducing cancer [23, 24]. Primrose oil containing large amounts of γ-linolenic acid mainly reduces pruritus and even then only if taken for several weeks [25].

Due in large part to the interest of the general population, scientific interest in other herbal drugs is currently increasing. To avoid adverse effects, many patients will accept a delayed onset of the desired effect. Preparations of chamomile, hamamelis and semi-synthetic tannin derivatives are being considered as possible alternatives to topical glucocorticoids in atopic dermatitis [21]. The results of preliminary studies of chamomile cream preparations in human volunteers [11, 12] and patients [5–7] are interesting. Few data about hamamelis preparations are available.

We have evaluated the antiinflammatory activity of three cream preparations containing hamamelis distillate in an exploratory study. Due to the mild effects expected, both following hydrocortisone and the herbal drugs, in addition to the conventional threshold ($P \leq 0.05$) a less strict statistical criterion ($P \leq 0.1$) was used. Effects lying between $0.05 < P \leq 0.1$ are called 'noteworthy'. Standard models of traumatised skin served for the induction of an inflammatory reaction. The stripping test of Wells [19] is particularly recommended for the evaluation of new drugs [26]. Although it cannot be excluded that skin blanching results only from vasoconstriction, this seems unlikely, since chamomile extract and hamamelis distillate (in contrast to hamamelis extract) are essentially free of vasoconstrictor tannins. Moreover, vasoconstriction following hydrocortisone 1% cream is very mild as compared to medium potency glucocorticoids [3]. Thus, the response to the drug should reflect true anti-inflammatory effect.

The activities of the test preparations were compared to their and other vehicles and creams containing chamomile extract and hydrocortisone 1%. One of the hamamelis distillate vehicles contained PC, which aids drug penetration into the skin [17]. Subjective (visual scoring) and objective parameters (Δa^* and ΔE^*) served for analysis. In general, chromametry turned out less discriminatory than visual inspection, as previously reported by Wilhelm et al. [27].

The suppression of the skin redness induced by UV irradiation and stripping of the horny layer was most pronounced following hydrocortisone 1% cream; P-values as compared to controls derived from visual scoring (stripping test, and Δa^* and ΔE^*) were below 0.1. Visual scoring also demonstrated a noteworthy anti-inflammatory activity of hamamelis PC cream (standard and high dosage) in stripped skin, although the latter was less potent than hydrocortisone. UV-induced erythema was best suppressed by hydrocortisone 1% cream and standard hamamelis

PC-cream while chamomile cream appeared inactive. The latter preparation was thus less potent against UV-induced erythema and about equipotent on stripped skin as compared to standard hamamelis PC-cream. The present result is well in accord with a clinical trial in eczema, which indicated a comparable antiphlogistic effect of cream preparations containing chamomile and hydrocortisone 0.25% [5].

As expected [17, 28], hamamelis PC-cream appeared more active than hamamelis cream. It is not clear whether the active ingredients of the PC-cream are encapsulated into liposome vesicles/nanoparticles. Although the phospholipids used should guarantee the presence of vesicles in the final preparation [29], this still needs definite proof. The lack of an increase in activity corresponding to the 4-fold increase in concentration suggests that the anti-inflammatory activity of the present preparation is close to a plateau.

In conclusion, the UV-induced erythema test and the cellophane tape stripping test demonstrated anti-inflammatory activity of topical hamamelis distillate, given that it is incorporated into a phospholipid-containing vehicle. Although less active than hydrocortisone cream, hamamelis PC-cream was superior to the respective base preparation. Therefore, hamamelis PC-cream may be suitable for the treatment of inflammatory skin disease, in particular atopic dermatitis, at least during the less severe phases of illness.

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