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Double-Blind, Randomized, Controlled Tolerability Trial of Six Hair Cleansing Products

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INTRODUCTION

Park Nicollet Contact Dermatitis Clinic ("PNCDC") was asked by WEN By Chaz Dean, Inc. ("WCD") to perform a clinical trial to assess the potential for a hair cleansing conditioner (HCC), WEN® by Chaz Dean (WCD®) Sweet Almond Mint Cleansing Conditioner, to cause contact dermatitis. As primary investigator for the PNCDC, I was informed of the following: (i) numerous consumer complained, and several lawsuits alleged, that the use of WCD® Sweet Almond Mint Cleansing Conditioner caused hair loss to consumers; (ii) in some of the lawsuits, the plaintiffs asserted a theory that their hair loss was caused by contact dermatitis, which was triggered by using WCD® Sweet Almond Mint Cleansing Conditioner; and (iii) the plaintiffs asserting the contact dermatitis theory have not presented any scientific support for their theory except to say that WCD® Sweet Almond Mint Cleansing Conditioner contains Methylchloroisothiazolinone/ Methylisothiazolinone (MCI/MI), also known as KathonCG, a recognized allergen. As a result of the assertion of this theory, WCD asked me to design a study to assess the potential for WCD® Sweet Almond Mint Cleansing Conditioner to cause contact dermatitis.

As an initial part of this assessment, I analyzed 33 individual ingredients in WCD® Sweet Almond Mint Cleansing Conditioner for sensitization (which analysis is the subject of a separate report). This analysis did not identify any obvious explanation for the consumer complaints or support for some of the plaintiffs' contact dermatitis theory.[1] This review did identify the following ingredients in WCD® Sweet Almond Mint Cleansing Conditioner which are known human sensitizers: Methylchloroisothiazolinone/ Methylisothiazolinone (MCI/MI),[2] stearamidopropyl dimethylamine (amidoamine),[3] and botanical/fragrance ingredients.[4] However, the presence of these ingredients were thought unlikely to be the major cause of the consumer complaints and do not support the plaintiffs contact dermatitis theory because: (i) these ingredients are commonly used in numerous personal care products; (ii) previous studies identified in a literature search indicate that primary sensitization to these allergens via wash-off hair cleansing products (e.g. hair cleansers) is unlikely;[5-6] and (iii) the concentrations of these ingredients in WCD® Sweet Almond Mint Cleansing Conditioner are at accepted levels.[7-8]

Thereafter, I designed the following protocol for, and initiated a human study involving 200 volunteers in a clinical trial to assess skin tolerability of WCD® Sweet Almond Mint Cleansing Conditioner as compared to 5 other hair cleansing products (HCPs). The goal of the clinical trial was to assess how WCD® Sweet Almond Mint Cleansing Conditioner compared to other HCPs for causing contact dermatitis, which some plaintiffs' counsel theorized caused their alleged hair loss.

BACKGROUND

Hair Cleansing Conditioners and WCD® Sweet Almond Mint Cleansing Conditioner

According to the literature, traditional shampoos are formulated with harsh sulfates and detergents, such as sodium lauryl sulfate, which remove sebum, sweat, environmental debris, and styling product residue from the scalp and hair shaft.[9] It has been reported that these traditional

[redacted]

shampoos can dry out the hair and scalp, causing hair frizz and breakage. An alternative method of cleansing hair are "cleansing conditioners" (also termed "conditioner washers" or "co-washes"), which are generally formulated without harsh sulfates and detergents that strip the hair of natural oils.[10] Originally developed for use by individuals with naturally curly or textured hair, HCC use has also grown among those with sensitive skin/hair and the general population. An informal Amazon search found over 30 products in the HCC category.[11]

Chaz Dean (President of WEN by Chaz Dean, Inc.) began developing the cleansing conditioner product in 1993 through a process of trial and error where he personally tested the development of the products on himself to identify the formulation that provided him with satisfactory results. The first of the WCD® Cleansing Conditioners, Sweet Almond Mint, officially launched in 1998. Over the next 10 years, WCD released additional versions of the Cleansing Conditioner line (e.g., Tea Tree, Cucumber Aloe, etc.). WCD's cleansing conditioner products are manufactured [redacted] based on WCD specifications [redacted] and the manufacturing method and chemical constituents of WCD® Sweet Almond Mint Cleansing Conditioner have not been modified or altered by WCD since they were finalized and entered into the marketplace.

In 2007, WCD licensed the product to the direct marketing company Guthy-Renker, Inc. ("GR") to distribute, market, manufacture and sell the product through various distribution outlets. , Since 2008, WCD has marketed and sold WCD® Sweet Almond Mint Cleansing Conditioner [redacted] through the QVC Home Shopping Network and GR independently manufactures the product pursuant to WCD's specifications and distributes everywhere else in the world. [redacted]

Background on Contact Dermatitis

Contact dermatitis may be irritant or allergic. Irritant contact dermatitis is a non-immunologic response dependent on many factors including endogenous (e.g. barrier function of the exposed skin, atopic status, age) as well as exogenous (e.g. concentration of the irritant, duration of exposure, heat, humidity, occlusion).[12,13] Common irritants include soaps and cleansers. Allergic contact dermatitis is a Type IV, delayed-type, cell-mediated allergic reaction. Common allergens include poison ivy, nickel, fragrance/botanical materials, and preservatives (including methylisothiazolinone and methylchloroisothiazolinone). Both allergic and irritant contact dermatitis may cause redness, swelling, pain, itching, blisters, and rash. Further, there have been reports that contact dermatitis has induced temporary hair shedding (telogen effluvium).[14]

METHODS

Overview

The purpose of this study was to evaluate skin responses to WCD® Sweet Almond Mint Cleansing Conditioner and compare these to skin responses to other HCPs on the market. This

[redacted]

double-blind, randomized, controlled clinical trial was approved by the Health Partners Institute Institutional Review Board and registered on ClinicalTrials.gov (NCT03483025). The study utilized two different standard skin tolerability tests: repeat open application test (ROAT)[15,16] and semi-open patch tests (SOPTs).[17] The six products tested included four HCCs (WCD® Sweet Almond Mint Cleansing Conditioner, [redacted]) and two HCP controls ([redacted] Shampoo as a "positive" control and [redacted] Shampoo ([redacted]) as a "negative" control). Study products were prepared in 1ml syringes (oral type). 0.2ml of each product was applied to 6 locations on the flexor forearms (for ROAT; increased duration over 5 weeks) and on the upper arms (for SOPT; week 4-5). Skin reactions were graded at baseline, week 2, week 4, and week 5.

The Test Materials

I am informed that WCD® Sweet Almond Mint Cleansing Conditioner was chosen because it is the product which has both been the most widely sold and received the most consumer complaints. The other 3 HCCs [redacted] were chosen based on greatest HCC market share and common availability [redacted] Shampoo was included as a "positive" control because it contains ingredients that are likely to cause irritant contact dermatitis (salicylic acid). [redacted] Shampoo [redacted] was chosen as mild/gentle "negative" control because it is formulated for use on babies.

Participants

Volunteers were recruited from the general population as well as employees/patients of Park Nicollet/Health Partners Clinics.

Inclusion criteria included:

- ≥18 years
- willingness to perform study procedures

Exclusion criteria included:

- Standard female study exclusions:
  1. breastfeeding females
  2. menstruating females of childbearing potential not willing to use a medically accepted method of contraception, during the study and up to 4 weeks after the end of study
  3. menstruating females of childbearing potential with a positive pregnancy test at randomization (per standard study protocols)

-Conditions which could interfere with clinical assessments of general tolerability:

1. presence of an overt bacterial, viral or fungal infection of the arms
2. history of bullous skin disorders, psoriasis, ichthyosis, and/or any other chronic skin condition (other than atopic dermatitis) which could result in skin barrier dysfunction

[redacted]

3. treatment with systemic immunosuppressive drugs within 2 weeks of enrollment

4. treatment with topical antibacterial, antimycotic, or immunosuppressive medications (including topical corticosteroids) on the forearms within 2 weeks of enrollment

5. use of over-the-counter moisturizer to the forearms in the 3 days prior to protocol commencement

6. previous positive patch test reaction to an ingredient present in any of the 6 HCPs

7. use of any other investigational agent in the 30 days prior to study commencement

Repeat Open Application Tests (ROATs)

Participants applied the 6 study products to 6 separate locations on the forearms (3 on the right and 3 on the left) using a standardized ROAT protocol.[15, 16,18] Clinical assessments (global as well as component score grading) were performed at 0, 2, 4, and 5 weeks.

ROAT Clinical Component Scoring*: This categorization was performed at each visit by a board-certified dermatologist investigator. Stopping point was a total score ≥6. Maximum total score of 10.

Sign/symptom	Score				
	0	1	2	3	4
Erythema	None	Slight redness (spotty or diffuse)	Moderate and uniform redness	Intense redness	Fiery redness
Scaling	None	Fine scaling	Moderate scaling	Severe with large flakes	N/A
Fissuring	None	Fine cracks	Single or multiple broader fissures	Wide cracks with hemorrhage or weeping	N/A

*Based on Frosch and Kligman[19]

ROAT Global Severity Score*: This categorization was performed at each visit by a board-certified dermatologist investigator. Stopping point was score ≥4.

0 (Negative): No reaction

1 (Doubtful): Very weak/slight erythema or scaling (spotty or diffuse)

2 (Weak): Weak/slight erythema, scaling, edema, or roughness

3 (Moderate): Moderate erythema, scaling, edema, or roughness or weak/slight erosions, vesicles or fissures

4: (Strong): Strong erythema, scaling, edema, or roughness or clear erosions, vesicles or fissures

5: (Very Strong/caustic): As 4, with necrotic areas
*Scoring of irritant reactions according to Loffler[20]

The site of application for each product was randomized. Participants and investigators were blinded to these locations. 0.2ml of each product was applied to the premoistened, designated test site of approximately 3 cm^2. For the first two weeks, the products were left in place on the skin for 5 minutes before rinsing off with running water. At the end of week 2, if the dermatologist investigator graded the total component score $\leq$5 and the global score $\leq$3, the application duration was increased to 10 minutes daily for weeks 3 and 4. At the end of week 4, if the dermatologist investigator graded the total component score $\leq$5 and the global score $\leq$3, the application duration was increased to 15 minutes daily for week 5. At any point, if the dermatologist investigator graded the total component score $\geq$6 or the global score $\geq$4, application of that specific study product was discontinued; duration escalation continued for all other study products not meeting these stopping criteria. No other soaps, moisturizers, or topical products were allowed on the ventral forearms during the study period.

Semi-Open Patch Tests (SOPTs)

In addition to the above ROAT protocol, at week 4, SOPTs were performed using the standard methodology of Dooms-Goosens.[17,21] Six 3 cm^2 circles were drawn on the upper arms with a surgical marker and 0.2ml of each study product was applied to the randomized designated area to create a thin film, blotted, allowed to dry for 5 minutes, and then covered with Scanpor tape (Norgesplaster Alpharma AS, Vennesla, Norway). The tape was kept in place for 48 hours and then removed at home by the participant.

The location of each product was randomized. Both participants and investigator were blinded to location of each product. These sites were graded at week 5 by the dermatologist investigator using a standardized patch test grading method.[22]

Semi-Open Patch Test Interpretation: North American Contact Dermatitis Group Grading Method

Negative (-) – normal skin
Doubtful (?) – macular erythema only
Mild (+) – erythema, infiltration, possibly papules
Moderate (++) – edematous or vesicular
Strong (+++) – spreading, bullous, ulcerative

Study Products

The six HCPs were packaged in identical 1ml capped oral-type tuberculin syringes (with no needles). Each syringe was pre-labeled with the forearm location for application per randomization (3 locations on right, 3 locations on left). Per standard clinical trial protocol, dispensing of study products was to insure enough product for application for the time between study visits. Three syringes for each product (total of 18 syringes) were dispensed at weeks 0 and 2 (2 weeks between study visits) Two syringes for each product (total of 12 syringes) were dispensed at week 4 (1 week between study visits).

[redacted]

Treatment Assignment, Blinding and Randomization

ROAT site allocation was determined by a computer-generated randomization log maintained by a non-blinded research assistant. After informed consent was obtained (and negative pregnancy test for women of childbearing potential), research personnel instructed the participant on how to perform the ROAT protocol and observed the first application. Written instructions were provided. The study products were applied daily and recorded in a patient diary. Participants were provided with written and oral instructions on completing the diary. The diary was evaluated at each visit and collected at the final visit. SOPT site allocation was determined by a computer-generated randomization log maintained by a non-blinded research assistant.

Concomitant Therapy

To avoid any confounding irritant exposures, participants were instructed to avoid use of prescription or nonprescription shampoos, cleansers, moisturizers, or any other topical medications to the forearms (during the entire study) and to the upper arms (for the final week of the study). Participants were able to use their normal shower/bath body cleansing product but were not allowed to apply these directly to the treatment areas (to avoid any confounding irritant exposures). Participants were able to shower/bathe throughout the study; during the first 48 hours of week 5 (when the SOPTs were covered with tape), participants showered/bathed with the tape in place.

Interruption or Discontinuation of Treatment

If the ROAT total component score reached $\geq$6 or the global score was $\geq$4 in a single test area ("stopping point"), application of that specific study product was discontinued per protocol. Participants were allowed to use 1% hydrocortisone cream or ointment, if desired, to that specific test site. Per protocol, duration escalation was continued at all other sites not meeting stopping criteria.

Treatment Compliance and Photography

Used and unused syringes were returned at each visit. Research assistants compared diary applications and used syringes for compliance. For additional documentation, photographs of the ROAT sites on forearms at were taken at weeks 2, 4, and 5 as well as the upper arm SOPT sites at week 5.

Visits and Assessments

Study week	**0 (Baseline)**	**2**	**4**	**5**
Inclusion/Exclusion Criteria	X			

Informed Consent	X			
History	X			
Women of Childbearing Potential: Urine Pregnancy Test	X			
Forearm ROAT Component Scoring (Erythema, Scaling, Fissuring)	X	X	X	X
Forearm ROAT Global Severity Assessment	X	X	X	X
Photography	X	X	X	X
Interim History and Adverse Events		X	X	X
Dispense Study Diary, Instructions, Witness First Application	X			
Dispense Study Cleansers	X	X	X	
Collect Study Cleansers		X	X	X
Diary Review		X	X	X
Upper Arm Semi-Open Patch Test Application			X	
Upper Arm Semi-Open Patch Test Component Scoring (Erythema, Scaling, Fissuring)				X
Upper Arm Semi-Open Patch Test Global Severity Assessment				X
Diary Collection				X

Outcome Measures

Primary study outcome: (week 5 or earlier per protocol):

- Intolerance – Defined as percentage of individuals with ROAT total component score ≥6 or ROAT global score ≥4

Secondary outcomes:

- ROAT
    1. Maximum ROAT Scores for each clinical component
        - Erythema
        - Scaling
        - Fissuring
    2. Percentage of "any reaction" (ROAT component score ≥1)
    3. Maximum ROAT global scores
- SOPT
    1. Maximum grade
    2. Percentage of ≥ "doubtful"
- Participant Characteristics
    1. Association of Fitzpatrick photoskin type[23] with tolerability
    2. Association of atopy with tolerability

[redacted]

Safety Assessments

Spontaneous reporting of local and systemic safety evaluations using the World Health Organization Scale were tabulated and categorized at each follow-up visit. Safety assessments consisted of monitoring and recording all adverse events, including serious adverse events. An adverse event was defined as any undesirable sign, symptom or medical condition occurring after starting study. This was intended to encompass all medical events during the trial. Medical conditions/diseases present before starting study treatment were only considered adverse events if they worsened after starting study treatment.

A serious adverse event was defined as an undesirable sign, symptom or medical condition which: 1. was fatal or life-threatening, 2. resulted in required or prolonged hospitalization, 3. resulted in persistent or significant disability/incapacity, 4. constituted a congenital anomaly or a birth defect, 5. was medically significant, in that it jeopardized the subject and required medical or surgical intervention to prevent one of the outcomes listed above.

Data Management and Statistical Methods

Analysis utilized a standard intent to treat approach. The primary endpoint was "stopping point" (ROAT total component score $\geq$6 or global $\geq$4 at any time; yes/no). Secondary endpoints included "any reaction" (ROAT component score $\geq$1 at any time; yes/no) and SOPT grade $\geq$ doubtful (yes/no). First, we summarized demographics and clinical variables by descriptive statistics: means and stand deviations for continuous variables and proportions for categorical variables. Chi-square tests were used to test associations of dichotomous endpoints with different cleanser products, atopy, and Fitzpatrick photoskin types.

Power Calculation

A sample size of 200 subjects was calculated to provide a 90% power for equivalency of WCD® Sweet Almond Mint Cleansing Conditioner and other study products using the dichotomous outcome "stopping point" (ROAT total component score $\geq$6 or global $\geq$4 at any time). This was based on the following assumptions: 1) an expected 30% of the non-atopics and 60% of atopics will reach "stopping point"; 2) enrollment of approximately 150 non-atopics and 50 atopics, and 2) a non-inferiority margin of 20%. If the WCD® Sweet Almond Mint Cleansing Conditioner product was slightly worse (3%) than the others, the sample size of 200 subjects would provide 80% power.

Data Management and Quality Assurance

Prior to the start of this study, the two board-certified dermatologist investigators correlated clinical scoring, thereby assuring consistency of clinical assessments. The same dermatologist performed ROAT clinical component scoring, ROAT global severity score assessments and SOPT scoring on a single patient, whenever possible. In the event that the dermatologist for that patient was unavailable for the study visit, the other dermatologist completed the assessments.

[redacted]

Data was collected on computer-generated case report data forms and entered into Access (Access 2010; Microsoft Corp, Redmond, WA). For quality assurance, data was double-entered; discrepancies were resolved by comparison with the paper record. Analyses were performed using the statistical software package SAS (SAS 9.2; SAS, Cary, NC).

RESULTS

Enrollment

298 participants were screened; 18 were excluded based on study criteria and 80 declined to participate (Figure 1). Enrollment occurred between April and October 2018; the last patient completed participation in November 2018. 200 participants were enrolled; all had study products dispensed and applied at the first visit. There was no data for ROAT and SOPT in 187 and 185 individuals, respectively (Figure 1).

Participant Characteristics

Most participants were female (81%) or Caucasian (Fitzpatrick phototypes I-III, 81%) (Table 1). Mean age was 48.7 years (standard deviation 16.5, range 18-88). This is similar to the demographics of individuals reporting adverse events to the FDA (98% female, median age 50, range 3-89 years, 85% Caucasian). Approximately one-third (39.5%) had a history of atopic dermatitis, asthma or hay fever.

ROAT Component Scores

All study products had at least one participant with erythema or scaling scores of >1 (Tables 2, 3). Only 2 products ([redacted]) produced fissuring (Table 4). The range for total component scores >1 were as follows: 1 for WCD® Sweet Almond Mint Cleansing Conditioner (2.1%); 1-2 for [redacted] (2.7%) and 1-2 for [redacted] (3.2%); 1-3 for [redacted] (9.1%); 1-6 for [redacted] (4.8%); and 1-9 for [redacted] (46.5%) (Table 5). Stopping point based on ROAT total component score of ≥6 was reached for only two products: [redacted] (0.5%) and [redacted] (9.1%).

ROAT Global Scores

The maximum global ROAT component scores >1 were as follows: 1 for WCD® Sweet Almond Mint Cleansing Conditioner (2.1%), 1 for [redacted] (2.7%), and 1 for [redacted] (3.2%); 1-2 for [redacted] Shampoo (9.1%); 1-3 for [redacted] (4.8%); and 1-4 for [redacted]

[redacted]

(46.5%) (Table 7). Stopping point based on ROAT Global score of ≥4 was reached for only [redacted] (3.7%).

Primary Outcome: ROAT Total Component Score ≥6 or Global Score ≥4

Only two products were stopped due to reaching the composite primary ROAT outcome of total component score >6 or global score ≥4: [redacted] (9.6%) (Figure 2) and [redacted] (0.5%). [redacted] was significantly less likely to be tolerated than all other products (p values <0.0001) (Table 8). There was no statistically significant difference in the tolerability of [redacted] as compared to the 4 HCPs (excluding [redacted]

ROAT Component ≥1

Using the minimal criteria of "any reaction" (ROAT component score ≥1 at any time), [redacted] was significantly less likely to be tolerated than all other products (p values <0.0001) (Table 8). WCD® Sweet Almond Mint Cleansing Conditioner was also significantly better tolerated than [redacted] Shampoo (p=0.01) There was no significant difference in tolerability of WCD® Sweet Almond Mint Cleansing Conditioner compared to the other 3 HCPs.

Semi-Open Patch Tests

All study products had at least one participant with at least one +/-? (doubtful) reaction on SOPT (Table 9). The frequency of any reaction was highest for [redacted] (7.1%, Figure 3) and lowest for WCD® Sweet Almond Mint Cleansing Conditioner (2.2%). As compared to [redacted] WCD® Sweet Almond Mint Cleansing Conditioner was significantly better tolerated as assessed by negative SOPT (p=0.04). There were no significant differences in the tolerability of WCD® Sweet Almond Mint Cleansing Conditioner compared to the other 5 HCPs.

Association of Atopy and Tolerability

There was no significant difference in the tolerability (defined as the minimal criteria of "any reaction" - ROAT component score ≥1 at any time) of any the study products based on history of atopic dermatitis (p values>0.48; data not shown). [redacted] however, was more likely to be stopped (ROAT total component ≥6 or global score ≥4 at any time) in individuals with a history of any atopic marker (atopic dermatitis, asthma, and/or hay fever) (p=0.02).

Association of Fitzpatrick Photoskin Type and Tolerability

[redacted] was significantly more likely to have "any reaction" (ROAT component Score of ≥1) in individuals with Fitzpatrick photoskin type I as compared to types II-VI (61.0% vs 42.5%, p=0.07). [redacted] was also more likely to be stopped (ROAT total

[redacted]

component ≥6 or global ≥4 at any time) in individuals with Fitzpatrick photoskin type I as compared to types II-VI (17.5% vs. 7.5%, approached statistical significance p=0.07). Comparisons of other Fitzpatrick photoskin types found only borderline significant association of having "any reaction" (ROAT component score of ≥1) to [redacted] Shampoo in individuals with Fitzpatrick photoskin type I/II as compared to types III-VI (12.6% vs 4.0%, p=0.06) and [redacted] in types IV-VI as compared to types I-III (9.1% vs 2.0% p=0.06). There were no other statistically significant differences in tolerability of any of the study products between Fitzpatrick photoskin types I-II vs. types III-VI or types I-III vs IV-VI.

Adverse Events

There were no serious adverse events. There were 12 participants who had adverse events, none of which required discontinuing the study. Ten were not study-related including 5 infections (urinary tract infection, gastrointestinal, mononucleosis, herpes simplex) and 5 injuries (bruise, finger trauma, punctured eardrum). Two adverse events (hives lasting 1 hour on right arm outside study site and an axillary fold rash outside study site) were thought to be possibly study related (possibly due to inadvertent transfer of study products).

DISCUSSION

This study has several important findings. First, the tolerability of WCD® Sweet Almond Mint Cleansing Conditioner, as measured by escalating duration ROAT, was comparable to 3 other HCCs and significantly better than both [redacted] and [redacted] shampoos. Second, the tolerability of WCD® Sweet Almond Mint Cleansing Conditioner, as measured by SOPT, was significantly better than [redacted] but not significantly different from the other 4 HCPs.

Expected Findings

It is not surprising that [redacted] had the highest rate of "any reaction" on both ROAT (46.5%) and SOPTs (7.1%). [redacted] contains 3% salicylic acid, an organic, beta-hydroxy acid derived from the willow tree. Salicylic acid functions in dermatologic preparations as a keratolytic, which removes scale and desquamating stratum corneum. As such, it is an irritant and is the most likely cause of the ROAT and SOPT reactions seen in this study. [redacted] contains benzyl salicylate, a preservative related to salicylic acid but which is much less irritating. Other ingredients in [redacted] which may cause irritation and/or allergy include the surfactants cocamidopropyl betaine[3] and sodium lauroyl sarcosinate.[24] These surfactants are less likely culprits given that these surfactants are also present in the other study products (Table 10) which did not have a high rate of reactions.

Unexpected Findings

In this study, [redacted] Shampoo was intended as a "negative control." Baby products, including shampoo, are generally perceived to be gentle, safe, and non-irritating preparations.[25]

[redacted]

Baby shampoo is commonly recommended for use on the eyelids as a treatment for blepharitis.[26] Because the amphoteric detergents used in baby shampoo act as an anesthetic to numb the eye tissues to prevent stinging, tissue damage may still occur but is not painful unless the anesthetic effect of the shampoo is no longer present.[9] In dermatology practice, it is not uncommon to see irritant eyelid dermatitis from baby shampoo used for blepharitis.[27] In addition, contact allergy to ingredients in baby shampoo, including amphoteric detergents (e.g. cocamidopropyl betaine[3]) and preservatives (e.g ethylhexylglycerin[28] and sodium benzoate[29]) have been reported.

Comparison of WCD® Sweet Almond Mint Cleansing Conditioner to other Hair Cleansing Conditioners

Traditional shampoos are formulated with detergents such as sodium lauryl sulfate which remove debris, oil, and materials from the scalp and hair shaft.[10] This can dry out the hair and scalp, causing frizz, scale, and hair breakage. HCCs are generally formulated without harsh detergents which strip the hair of natural oils. [10] This study found that there was no statistically significantly differences in the tolerability of WCD® Sweet Almond Mint Cleansing Conditioner as compared to the other 3 HCCs. The general composition of these HCCs are similar although the specific surfactants, preservatives, and fragrances vary (Table 10).

SOPT

The SOPT is typically used for assessment of allergic contact dermatitis to wash-off products.[17, 21] Individuals with a history of allergic reactions to HCPs were excluded from this study. Therefore, a low rate of SOPT reactions would be expected. An indurated, papulovesicular/bullous reaction (Grade ++ or +++) would indicate sensitization to an ingredient in the product during the study. A doubtful, macular erythema reaction (Grade +/-?) would most likely represent mild irritation. Grade + reactions are generally accepted as allergic, although many are not reproducible.[30] In this study, all 6 HCPs had at least 3 doubtful (?) reactions ([redacted] and [redacted] [n=3 each]; WCD® Sweet Almond Mint Cleansing Conditioner and [redacted] [n=4 each]; [redacted] [n=5]; [redacted] [n=11]). Only 4 HCPs had a SOPT score of + ([redacted] [n=1]; [redacted] [n=2 each]). No HCPs had a score of ++ or +++. Review of the photographs of the SOPTs with grade of + found that only two were suggestive of an allergic reaction and both of these were to [redacted] (Figure 3).

Atopy

Individuals with atopic dermatitis are recognized to have impaired skin barrier abnormalities including filaggrin mutations.[31] This leads to increased transepidermal water loss, penetration of irritants and allergens, and triggering of immune responses. Hay fever and asthma are major criteria for establishing the diagnosis of atopic dermatitis due to significant association between these conditions.[32]

[redacted]

Atopic dermatitis was not statically associated with an increased frequency of "any reaction" (ROAT component score ≥1 at any time) to any of the 6 study products; while the frequency of primary outcome measure (ROAT total component ≥6 or global score ≥4 at any time) was higher in individuals with atopic dermatitis as compared to those without (15.4% vs. 9.2%), this was not statistically significant. This may be due to small numbers of individuals with atopic dermatitis (n=13).

When comparing individuals with atopy (atopic dermatitis, asthma, and/or hay fever) to those without, the frequencies of "any reaction" were higher for almost all study products in atopics but none were statistically significant. [redacted] however, was significantly more likely to be stopped (ROAT total component ≥6 or global score ≥4 at any time) in atopic individuals. These findings are not surprising due to the known barrier dysfunction and susceptibility to irritants in atopic dermatitis.[31]

Photosensitivity Skin Type

While several studies have compared skin responses to irritants in different races (Caucasian, Asian, Black) with conflicting results,[33] less is known about specific Fitzpatrick photoskin types and irritation. In this study, [redacted] was more likely to have "any reaction" (ROAT component score of ≥1) in individuals with Fitzpatrick photoskin type I as compared to types II-VI (61.0% vs 42.5%, approached statistical significance p=0.07). [redacted] was also more likely to be stopped (ROAT total component ≥6 or global score ≥4 at any time) in individuals with Fitzpatrick photoskin type I as compared to types II-VI (17.5% vs. 7.5%, approached statistical significance p=0.07). Comparisons of other Fitzpatrick photoskin types found only borderline associations of having "any reaction" (ROAT component score of ≥1) to [redacted] Shampoo in individuals with Fitzpatrick photoskin type I/II as compared to types III-VI (12.6% vs 4.0%, p=0.06).

These findings are consistent with a French study of over 10,000 patients which found that fair skin type was associated with skin sensitivity.[34] Similarly, separate studies of 44 Caucasian individuals[35] and 23 females[36] found significant correlations between low minimal erythema dose and greater response to irritants. Fitzpatrick photoskin type I was found to be associated with higher likelihood for irritation to sodium lauryl sulfate in 23 females.

While previous studies have found statistically different rates of positive patch test reactions to specific allergens between black and white patients suspected of having ACD, the etiology of these differences is most likely culturally determined exposure patterns rather than genetic differences.[37]

Limitations

This study has several limitations. First, testing of multiple products on the scalp is logistically difficult; therefore we used the standard methodology of testing products on the flexor forearms.

[redacted]

Second, this study was not designed specifically to assess hair loss directly; it was designed to assess the tolerability of WCD® Sweet Almond Mint Cleansing Conditioner as compared to 3 other HCCs as well as 2 shampoos, Contact dermatitis (irritant or allergic) has been the alleged cause of hair loss in some consumer complaints. Finally, this study excluded individuals with a history of a positive patch test reaction to an ingredient in any of the 6 HCPs; as may occur with any product, it is possible some consumer-reported skin reactions were due to allergic reactions in individuals previously sensitized to an ingredient in WCD® Sweet Almond Mint Cleansing Conditioner. Importantly, the composition of WCD® Sweet Almond Mint Hair Cleansing Conditioner is very similar to other HCPs on the market.

SUMMARY

This double blind, randomized, controlled study used both SOPTs and ROAT duration escalation over a 5 week protocol to assess tolerability of 6 different hair cleansing products. 9.6% of participants achieved ROAT stopping point for one product ([redacted] only one other HCP ([redacted]) was discontinued. [redacted] had a significantly higher frequency of "any reaction" for ROAT (46.5% vs. ≤9.1%) and SOPT (6.0% vs. ≤2.7%) than the other 5 products. WCD® Sweet Almond Mint Cleansing Conditioner had corresponding "any reaction" frequencies of 2.7% (ROAT) and 2.2% (SOPT). WCD® Sweet Almond Mint Cleansing Conditioner was significantly better tolerated than both [redacted] and [redacted] Shampoo and was similar in tolerability to the other 3 hair cleansing conditioners.

CONCLUSIONS

This study found no evidence of allergic sensitization or irritant contact dermatitis to WCD® Sweet Almond Mint Cleansing Conditioner in 200 individuals. The results demonstrate that WCD® Sweet Almond Mint Cleansing Conditioner is a non-irritating cleanser, and better tolerated than [redacted] Shampoo, a well-known gentle hair cleanser intended for use on babies. [redacted] caused significant irritation (reaching stopping point in 9.6% of individuals). If contact dermatitis was the inciting factor for hair loss (as has been alleged in some consumer complaints), this study suggests that WCD® Sweet Almond Mint Cleansing Conditioner would not be expected to be a cause for hair loss in the general population. This study demonstrates that the tolerability of WCD® Sweet Almond Mint Cleansing Conditioner is similar to other cleansing conditioners on the market, whose use has not been associated with an increased adverse events such as hair loss in the general population

These findings are further supported by other studies previously performed on WCD® Sweet Almond Mint Cleansing Conditioner which have also found no obvious explanation for consumer complaints as summarized below:

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- Toxicological hazard assessment by Cardno ChemRisk® of the individual ingredients of the Product, which no evidence that the formulation and ingredient concentrations (all <10%, other than water) would be expected to cause skin irritation, skin sensitization, or hair loss.[38]

- Skin irritation hazard assessment of the WCD® Sweet Almond Mint Cleansing Conditioner's ingredients found that the irritation potential of the product was low and similar to other HCPs on the market.[39]
- An evaluation of 30 ingredients in 3 separate WCD® HCCs (including the Product) using the National Library of Medicine's Household Products Database and the Environmental Working Group's Skin Deep Cosmetic Database found that more than 20,000 personal care products (of the approximately 70,000 in the database) contained one or more of the ingredients, indicating wide use of these substances. [40]
- Six ingredients (behentrimonium methosulfate, dicetyldimonium chloride, methylchloroisothaizolinone, methylisothiazolinone, panthenol, and stearamidopropyl dimethylamine) in WCD® HCCs were evaluated using two *in vitro* tests. The OECD 439 EpiDerm Skin Irritation Test (SIT) utilizes a reconstructed human epidermis to evaluate the irritation potential of a test article. The OECD 442C, Direct Peptide Reactivity Assay (DPRA) utilizes high-performance liquid chromatograph to evaluate test article-peptide reactivity to examine sensitization potential.[41] These *in vitro* tests found minimal irritation and low peptide reactivity.[42]
- Since 2006, a certified testing facility performed human repeat insult patch tests with a variety of WCD® products, including the Product, in over 2600 people. Patches with WCD® products were occluded for 24 hours and reapplied 3 times per week for 3 weeks. 10-14 days later, a retest patch was applied to previously unexposed test areas and evaluated at 48 and 96 hours later. Neither skin irritation nor sensitization was observed in any volunteer.[43]
- A single-blind, randomized, controlled study of the WCD® Sweet Almond Mint Cleansing Conditioner in 142 volunteers found no increased hair loss.[44]
- Review of the ingredients in WCD® Sweet Almond Mint Cleansing Conditioner did not identify any ingredients that significantly differ from other HCCs in likelihood of causing contact dermatitis.[1]

The current clinical trial found no evidence that WCD® Sweet Almond Mint Cleansing Conditioner differs from 3 other HCCs in likelihood of causing contact dermatitis; WCD® Sweet Almond Mint Cleansing Conditioner was better tolerated than a widely used baby shampoo.

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