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Effect of Sunscreen Application Under Maximal Use Conditions on Plasma Concentration of Sunscreen Active Ingredients

A Randomized Clinical Trial

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Key Points

Question What is the maximum plasma concentration of active ingredients of various types of sunscreen formulations under maximal use conditions?

Findings In this randomized clinical trial that included 24 healthy participants and application of 4

Findings In this randomized clinical trial that included 24 healthy participants and application of 4 commercially available sunscreen formulations, maximum plasma concentrations (geometric mean [coefficient of variation]) for the active ingredient avobenzone were 4.0 (60.9%), 3.4 (77.3%), 4.3 (46.1%), and 1.8 (32.1%) ng/mL for 2 different sprays, a lotion, and a cream, respectively.

Meaning The systemic absorption of sunscreen active ingredients supports the need for further studies to determine the clinical significance of these findings.

Abstract

Importance The US Food and Drug Administration (FDA) has provided guidance that sunscreen active ingredients with systemic absorption greater than 0.5 ng/mL or with safety concerns should undergo nonclinical toxicology assessment including systemic carcinogenicity and additional developmental and reproductive studies.

Objective To determine whether the active ingredients (avobenzone, oxybenzone, octocrylene, and ecamsule) of 4 commercially available sunscreens are absorbed into systemic circulation.

Design, Setting, and Participants Randomized clinical trial conducted at a phase 1 clinical pharmacology unit in the United States and enrolling 24 healthy volunteers. Enrollment started in July 2018 and ended in August 2018.

Interventions Participants were randomized to 1 of 4 sunscreens: spray 1 (n = 6 participants), spray 2 (n = 6), a lotion (n = 6), and a cream (n = 6). Two milligrams of sunscreen per 1 cm^2 was applied to 75% of body surface area 4 times per day for 4 days, and 30 blood samples were collected over 7 days from each participant.

Main Outcomes and Measures The primary outcome was the maximum plasma concentration of avobenzone. Secondary outcomes were the maximum plasma concentrations of oxybenzone, octocrylene, and ecamsule.

Results Among 24 participants randomized (mean age, 35.5 [SD, 1.5] years; 12 (50%] women; 14 [58%] black or African American; 14 [58%]), 23 (96%) completed the trial. For avobenzone, geometric mean maximum plasma concentrations were 4.0 ng/mL (coefficient of variation, 6.9%) for spray 1; 3.4 ng/mL (coefficient of variation, 77.3%) for spray 2; 4.3 ng/mL (coefficient of variation, 46.1%) for lotion; and 1.8 ng/mL (coefficient of variation, 32.1%). For oxybenzone, the corresponding values were 209.6 ng/mL (66.8%) for spray 1, 194.9 ng/mL (52.4%) for spray 2, and 169.3 ng/mL (44.5%) for lotion; for octocrylene, 2.9 ng/mL (102%) for spray 1, 7.8 ng/mL (113.3%) for spray 2, 5.7 ng/mL (66.3%) for lotion, and 5.7 ng/mL (47.1%) for cream; and for ecamsule, 1.5 ng/mL (166.1%) for cream. Systemic

concentrations greater than 0.5 ng/mL were reached for all 4 products after 4 applications on day 1. The most common adverse event was rash, which developed in 1 participant with each sunscreen.

Conclusions and Relevance In this preliminary study involving healthy volunteers, application of 4 commercially available sunscreens under maximal use conditions resulted in plasma concentrations that exceeded the threshold established by the FDA for potentially waiving some nonclinical toxicology studies for sunscreens. The systemic absorption of sunscreen ingredients supports the need for further studies to determine the clinical significance of these findings. These results do not indicate that individuals should refrain from the use of sunscreen.

Trial Registration ClinicalTrials.gov Identifier: NCT03582215

Introduction

Sunscreens prevent skin damage by reflecting, absorbing, and/or scattering UV radiation and are regulated as over-the-counter (OTC) drug products in the United States.[1-4] For some individuals, sunscreen products may be applied in substantial amounts multiple times every day over the course of a lifetime as both primary sunscreen products, starting from an age of 6 months, and as ingredients in cosmetic products.[5] Application to the skin can result in multiple grams of sunscreen being applied in a day, even with modest use.[5] Although OTC sunscreen products are widely used, little is known about systemic exposure for most active ingredients.[6] Understanding the extent of systemic exposure of these products is important, as even a low percentage of systemic absorption (eg, 0.1%) could represent a significant systemic exposure (eg, milligrams of ingredient being systemically absorbed per day).[5] The clinical relevance of systemic exposure is not well understood.

The US Food and Drug Administration (FDA) guidance titled "Guidance for Industry: Nonprescription Sunscreen Drug Products Safety and Effectiveness Data" (sunscreen guidance)[1] recommends an assessment of the human systemic absorption of sunscreen ingredients with a maximal usage trial[7,8] and a nonclinical safety assessment including dermal carcinogenicity and embryofetal toxicity. The FDA sunscreen guidance[1] and the proposed rule for the OTC sunscreen monograph[6] note that some nonclinical toxicology studies (ie, systemic carcinogenicity and additional developmental and reproductive studies) may be waived if results of an adequately conducted human pharmacokinetic maximal usage trial show a steady state blood level less than 0.5 ng/mL and an adequately conducted toxicology assessment does not reveal any potential safety concerns.[9,10] The objective of the current study was to determine the systemic exposure of active ingredients (avobenzone, oxybenzone, octocrylene, and ecamsule) present in 4 commercially available sunscreen products of different formulation types under maximal usage conditions.

maximal usage conditions.

Methods

Study Design

The study protocol was approved by the FDA Research in Human Subjects Committee and the clinical site's local institutional review board (Advarra [https://www.advarra.com]). All participants provided written informed consent. The protocol and statistical analysis plan are available in **Supplement 1**.

This was an open-label, randomized, 4-group parallel study conducted at a phase 1 clinical pharmacology unit in the United States to evaluate the effects of multiple applications of 4 different topical sunscreen formulations (eTable 1 in **Supplement 2**) in healthy adult participants (**Table 1**; eTable 2 in **Supplement 2**; deidentified participant data available in **Supplement 3**). Study participants remained in the clinic for up to 7 days and were not exposed to direct sunlight during the study. The study product was weighed in advance and applied by a qualified study team member. Each group had 6 participants (3 men, 3 women) who received a single formulation. Thirty blood samples were collected over 7 days (day 1: 0, 0.5, 1, 1.5, 2, 4, 6, 8, 9, 10, 12, and 14 hours after first sunscreen application; day 2: 23, 28, and 33 hours; day 3: 47, 52, and 57 hours; day 4: 71, 73, 74, 76, 78, 81, 82, 84, and 86 hours; day 5: 95 hours; day 6: 120 hours; and day 7: 144 hours). Two milligrams of sunscreen per 1 cm^2 was applied to 75% of body surface area (area outside of normal swimwear; see Pharmacy Manual in **Supplement 1**) 4 times per day for 4 days (at 0, 2, 4, and 6 hours on day 1; 24, 26, 28, and 30 hours on day 2; 48, 50, 52, and 54 hours on day 3; and 72, 74, 76, and 78 hours on day 4; see Pharmacy Manual in **Supplement 1**). This application regimen was chosen because sunscreens are labeled to be applied at least every 2 hours and may be applied for multiple days in a row, such as might occur when outside in the sun. Plasma concentrations of each active ingredient were assessed with validated liquid chromatography with tandem mass spectrometry methods[11] (eMethods 1-3 in **Supplement 2**).

Participants Population

The study participants were enrolled from July to August 2018. Participants were recruited by standard recruiting for a phase 1 healthy volunteer study (ie, email, text, online). Self-identified race/ethnicity was collected in an open-ended format and recorded by clinical staff as a standard component of a clinical trial.[12] In addition, Fitzpatrick skin type[13] was recorded by clinical staff. Key inclusion criteria were ages 18 through 60 years with a body mass index of 18.5 to 29.9 (calculated as weight in kilograms divided by height in meters squared), negative test results for alcohol and drugs of abuse, and no known or suspected allergies or sensitivities to any components of the sunscreen formulations (additional details available in the study protocol in **Supplement 1**).

The major exclusion criteria were participants with broken, irritated, or unhealed skin or active sunburn

and active autoimmune disease, anemia, or other chronic condition that affects blood sample collection. Additionally, participants using any of the listed sunscreen products or products containing the listed active ingredients were excluded from enrollment.

Randomization

After screening, the 24 participants were randomized to participate in 1 of the 4 treatment groups (**Figure 1**). The randomization code was generated by a validated database system. Randomization was conducted in block sizes of 4 and included equal numbers of women and men in each treatment group. This study was unblinded to investigators and participants because of the distinct differences between formulations (ie, spray vs lotion or cream), although participants and investigators did not know which spray or which lotion vs cream they received. Allocation concealment was not performed, and bioanalytical laboratory personnel were not blinded to allocation.

Outcomes

The prespecified primary outcome was the maximum plasma concentration of avobenzone over days 1 through 7. Avobenzone is one of the primary UVA filters in the OTC sunscreen monograph,[6] and systemic exposure data for this compound did not exist. The secondary outcomes were the maximum plasma concentrations of oxybenzone, octocrylene, and ecamsule over days 1 through 7.

Along with the primary and secondary outcomes, other exploratory pharmacokinetic parameters were calculated, including time of maximum concentration overall and on days 1 and 4, area under the curve (AUC) of plasma concentration vs time overall and on days 1 and 4, trough concentration or residual concentration each day, and terminal half-life (time required for active ingredient concentration to decrease by 50% during the terminal or final decline phase). All adverse events, whether serious or nonserious and whether related to the study drug, were recorded by study personnel and adjudicated by the principal investigator. No adverse events of special interest were specified.

Two post hoc assessments were performed. The number and percentage of participants with plasma concentrations of active ingredient exceeding 0.5 ng/mL were summarized based on day-1 observations. In addition, accumulation with repeat dosing was assessed by the log-transformed ratio of maximum plasma concentration and AUC on day 4 vs 1.

Statistical Analysis

Because this was an exploratory study to assess general methodology for a sunscreen maximal usage trial and no prior data existed on the systemic absorption of avobenzone, the sample size was determined empirically with reference to the sunscreen guidance recommendation for pilot studies.[7] Data are reported with standard descriptive statistics for all demographics (arithmetic means) and pharma-

cokinetic parameters (geometric mean, coefficient of variation, confidence intervals, minimum, and maximum). Terminal half-life is reported only for participants with 3 or more concentration values in the terminal portion of the curve and an adjusted coefficient of determination (R^2) greater than 0.70.

In post hoc analyses, accumulation with repeat dosing was assessed by log-transforming AUC and maximum plasma concentration from day 1 and 4 for each product and active ingredient. Data were analyzed using a linear-mixed effects model with fixed effects for day (day 4 vs day 1) and random effects for participant. Point estimates and corresponding 2-sided 90% CIs were obtained from the model and exponentiated to provide estimates of the geometric mean ratio and 90% CI of the ratio; 90% CIs were chosen because they are standard in pharmacokinetic studies.[14,15] Exposures on day 4 vs day 1 were considered not significantly different if the lower bound of the 90% CI for all exposure metrics included 1.

Plasma concentrations below the limit of quantitation were assigned as zero during calculation of pharmacokinetic parameters. No adjustments for multiplicity were made in the statistical analyses. Because of the potential for type 1 error due to multiple comparisons, findings for analyses of secondary outcomes, exploratory pharmacokinetic parameters, and post hoc assessments should be interpreted as exploratory. Standard noncompartmental calculations of pharmacokinetic parameters and statistical analyses were performed in R version 3.4.3 (R Foundation).

Results

Twenty-four participants (mean age, 35.5 [SD, 10.5] years; 12 [50%] women); 14 [58%] black or African American; 14 [58%] Fitzpatrick skin type 5 or 6) were randomized to 4 sunscreen products (**Table 1**, **Figure 1**). Spray 1 contained 3% avobenzone, 6% oxybenzone, 2.35% octocrylene, and 0% ecamsule; spray 2 contained 3% avobenzone, 5% oxybenzone, 10% octocrylene, and 0% ecamsule; the lotion contained 3% avobenzone, 4% oxybenzone, 6% octocrylene, and 0% ecamsule; and the cream contained 2% avobenzone, 0% oxybenzone, 10% octocrylene, and 2% ecamsule (**Table 1**).

All participants completed the study except 1 participant receiving the cream, who discontinued on day 2 because of milia. The most common adverse event was rash, which developed in 1 participant (17%) in each group. Adverse events, which included rash, milia, and pruritis, resolved in all participants (all adverse events are listed in eTable 4 in **Supplement 2**).

Approximately 17% of measures (91/540 samples) were below the lower limit of quantitation for spray 1, 13% (68/540 samples) for spray 2, 13% (68/540 samples) for lotion, and 33% (167/501) for cream. All data from the 1 participant who discontinued from the study were included in the analysis up through the last available time point (47 hours).

Avobenzone

All 4 sunscreen products resulted in avobenzone exposures, with plasma concentrations exceeding 0.5 ng/mL on day 1 for all products and through day 7 for all products except the cream (**Figure 2**, **Table 2**; eTable 3 in **Supplement 2**). Geometric mean maximum plasma concentrations were 4.0 ng/mL (coefficient of variation, 60.9%) for spray 1; 3.4 ng/mL (coefficient of variation, 77.3%) for spray 2; 4.3 ng/mL (coefficient of variation, 46.1%) for lotion; and 1.8 ng/mL (coefficient of variation, 32.1%) for cream (**Table 2**). AUC and maximum plasma concentration increased from day 1 to day 4 for all 4 products (**Table 2**; eTable 5 in **Supplement 2**), consistent with drug accumulation. All formulations had exposure exceeding 0.5 ng/mL on day 1, with the majority of participants reaching that threshold within 6 hours after the first application (**Table 3** and **Figure 3**). There was a long terminal half-life (mean range, 33-55 hours) (**Table 2**).

Oxybenzone

All 3 products with oxybenzone resulted in oxybenzone exposure, with plasma concentrations exceeding 20 ng/mL on day 7. Geometric mean maximum plasma concentrations were 209.6 ng/mL (coefficient of variation, 66.8%) for spray 1; 194.9 ng/mL (coefficient of variation, 52.4%) for spray 2; and 169.3 ng/mL (coefficient of variation, 44.5%) for lotion (**Table 2**). AUC was numerically higher on day 4 compared with day 1 for all 3 products, consistent with drug accumulation, although only spray 1 and lotion had 90% CIs excluding unity (**Table 2**; eTable 5 in **Supplement 2**). All participants who received formulations containing oxybenzone had plasma concentrations exceeding 0.5 ng/mL within 2 hours after a single application on day 1 (**Table 3** and **Figure 3**). There was a long terminal half-life (mean range, 24-31 hours) (**Table 2**).

Octocrylene

All 4 products resulted in octocrylene exposures, with plasma concentrations exceeding 0.5 ng/mL, starting from day 1 and lasting through day 7. Geometric mean maximum plasma concentrations were 2.9 ng/mL (coefficient of variation, 102%) for spray 1; 7.8 ng/mL (coefficient of variation, 113.3%) for spray 2; 5.7 ng/mL (coefficient of variation, 66.3%) for lotion; and 5.7 ng/mL (coefficient of variation, 47.1%) for cream (**Table 2**). AUC increased from day 1 to day 4 for all 4 products, and maximum plasma concentration was numerically higher on day 4 compared with day 1 (**Table 2**; eTable 5 in **Supplement 2**), consistent with drug accumulation. All participants who received the 3 products with the highest octocrylene product composition (spray 2, lotion, cream) had octocrylene plasma concentrations exceeding 0.5 ng/mL within 6 hours of the first administration (**Table 3** and **Figure 3**). There was a long terminal half-life (mean range, 42-84 hours) (**Table 2**).

Ecamsule

The cream was the only product containing ecamsule. The geometric mean maximum plasma concentration was 1.5 ng/mL (coefficient of variation, 166.1%) (**Table 2**). Five of 6 participants had an ecamsule plasma concentration exceeding 0.5 ng/mL on day 1 (**Table 3** and **Figure 3**). Some pharmacokinetic measures could not be calculated because 109 of 167 time points were below the assay limit of quantitation (0.2 ng/mL).

Discussion

This randomized clinical trial demonstrated systemic exposure of 4 commonly used sunscreen active ingredients on application of sunscreen products under maximal use conditions consistent with current sunscreen labeling (ie, apply at least every 2 hours). All 4 sunscreen active ingredients tested resulted in exposures exceeding 0.5 ng/mL. The clinical effect of plasma concentrations exceeding 0.5 ng/mL is unknown, necessitating further research.

Absorption of some sunscreen ingredients has been detected in other studies; however, significant data gaps exist.[16-18] In the recent FDA proposed rule for the OTC monograph,[6] 2 active ingredients (zinc oxide and titanium dioxide) were found to be generally recognized as safe and effective, while for 12 active ingredients (cinoxate, dioxybenzone, ensulizole, homosalate, meradimate, octinoxate, octisalate, octocrylene, padimate O, sulisobenzone, oxybenzone, and avobenzone) there were insufficient data to make a "generally recognized as safe and effective" determination; thus, more data have been requested from the manufacturers. Avobenzone, oxybenzone, and octocrylene were part of the present study; of note, ecamsule is marketed under a New Drug Application and is not part of the OTC monograph.

Oxybenzone, along with some other sunscreen active ingredients including octocrylene, has been found in human breast milk.[19] In addition, oxybenzone has been detected in amniotic fluid, urine, and blood.[6] Furthermore, some studies in the literature have raised questions about the potential for oxybenzone to affect endocrine activity.[6,20] No prior plasma concentration data existed for avobenzone or octocrylene, while ecamsule use was shown to result in limited but detectable exposure in a study conducted under what would be considered submaximal usage conditions today.[21] Currently, multiple active ingredients lack nonclinical safety assessment data, including systemic carcinogenicity and additional developmental and reproductive studies to determine the clinical significance of the level of absorption of sunscreen active ingredients.

This study was performed to demonstrate the feasibility of conducting a sunscreen maximal usage trial[7] and obtain preliminary data on sunscreen active ingredients. It was not intended to be a definitive maximal usage trial study. In this study, a total of 6 participants per formulation was sufficient to detect systemic exposure exceeding 0.5 ng/mL for the tested ingredients but not to delineate the

absorption across the entire potential population that uses sunscreens.

The 0.5-ng/mL threshold is based on the principle that the level would approximate the highest plasma level below which the carcinogenic risk of any unknown compound would be less than 1 in 100 000 after a single dose.[1,6] This Threshold of Toxicological Concern (TTC) concept was first adopted by FDA in the regulation of food packaging substances that can migrate into food.[9] The threshold value is also consistent with the TTC applied to pharmaceutical drug substance impurities in the International Council for Harmonisation "Guidance for Industry: M7 (R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk."[10] That document recommends a TTC of 1.5 µg/d, when appropriate, which was translated to 0.5 ng/mL for sunscreen active ingredients, assuming a circulating plasma volume of approximately 3 L. Application of this concept was considered acceptable during the determination of the "generally recognized as safe and effective" status of sunscreen active ingredients because such ingredients will be supported by extensive human use and absence of other pharmacologic or toxicologic signals from the nonclinical assessment recommended in the FDA sunscreen guidance. Application of such a threshold concept might not be appropriate or clinically meaningful for chemicals or chemical classes with effects on the human body, beyond that intended as sunscreen.

While the current study was purposefully designed to represent maximal usage per sunscreen labels (ie, apply at least every 2 hours) to areas of the body outside of normal swimwear over multiple days as might occur at the beach, absorption exceeding 0.5 ng/mL occurred on day 1 (**Figure 3** and **Table 3**) and for 3 of the 4 active ingredients lasted until day 7 (**Figure 2**). A second phase of this study will use a different design to investigate additional questions raised by this study, including the maximum plasma concentration after a single application, the skin concentration during the washout phase, the plasma concentration up to 17 days after the last dose, and the systemic exposure to additional commonly used sunscreen ingredients, including octinoxate, homosalate, and octisalate.

Limitations

This study has several limitations. First, the study was conducted in indoor conditions without exposure to heat, sunlight, and humidity, which may alter or modify the rate of absorption of sunscreen active ingredients. While this is a limitation, the study was designed to collect informative data in a standardized manner to design subsequent studies. Second, the study was not designed to assess differences in absorption by formulation type, Fitzpatrick skin type, or participant age. However, as shown in the individual participant absorption profiles (**Figure 2** and **Figure 3**), there was consistent absorption of multiple sunscreen active ingredients across the different formulation types, Fitzpatrick skin types, and ages in the study. Third, the study was conducted with multiple applications of sunscreen products as per the labeled dosage regimen and not evaluated on single-dose application, so maximum plasma

concentration and additional pharmacokinetic characteristics after a single application were not determined in this study.

Conclusions

In this preliminary study involving healthy volunteers, application of 4 commercially available sunscreens under maximal use conditions resulted in plasma concentrations that exceeded the threshold established by the FDA for potentially waiving some nonclinical toxicology studies for sunscreens. The systemic absorption of sunscreen ingredients supports the need for further studies to determine the clinical significance of these findings. These results do not indicate that individuals should refrain from the use of sunscreen.

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