Title: Pilot Studies Testing Use of Topical Imipramine in Reducing Ultraviolet B Induced Microvesicle Particle Release in Photosensitive Subjects

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INFORMED CONSENT AND AUTHORIZATION

PILOT STUDIES TESTING USE OF TOPICAL IMIPRAMINE IN REDUCING ULTRAVIOLET B INDUCED MICROVESICLE PARTICLE RELEASE IN PHOTOSENSITIVE SUBJECTS

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Sponsor(s) name and address:

National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20892

Site(s) where study is to be conducted:

Wright State Physician's Building
725 University Blvd
Dayton Ohio 45435

Phone number for subjects to call for questions:

Subjects can call the Pharmacology Translational Unit at (937) 245-7500 or (937) 775-2463

Key Information Summary

The purpose of this study is three-fold. First, we will assess whether subjects who have clinically abnormal reactions to sunlight (photosensitivity) have increased levels of microvesicle particles (MVP) following ultraviolet B (UVB) treatment to localized area of

skin. Second, we will assess if topical application of the medicine imipramine will block UVB-induced MVP release. Third, we will assess if imipramine will block UVB-induced increased erythema reactions (reddening of the skin). The use of imipramine in this study is considered investigational, meaning it has not been approved by the FDA for marketing in the United States for the use being tested in this research. However, topical imipramine is commonly used in topical anti-itch and anti-pain creams.

If you agree to be in this study the following will happen:

Your participation in this study will require 4 visits over 4 days.

Day 0: (6 hrs)

1. Informed Consent.
2. Fill out Photosensitivity Questionnaire.
3. Testing skin type by measuring redness/pigmentation on inner arm.
4. Photography then UVB treatment to inner forearm skin and back.
5. Imipramine or control (without imipramine) application to skin.
6. Return to clinic in 4 hours for removal of topical application, photography, and to measure skin redness and for study staff to obtain four skin biopsies of forearm.

Day 1: (30-60 minutes)

Return to clinic for photography and to measure skin redness on the back

Day 3: (30-60 minutes)

Return to clinic for photography and to measure skin redness on the back

Potential risks you may experience include:

- Exaggerated response to UVB treatment (sunburn)
- Risk of allergic reaction of imipramine
- Skin biopsy risks: allergic reaction to the local anesthetic lidocaine, risk of small scar at biopsy site

Additional risks are listed on page 7.

Benefits

You may not benefit by participating in this study. The information collected may not benefit you directly; however, the information may be helpful to others by providing us with an understanding of how sunlight and imipramine can have effects on the human body.

Alternatives

This study is not a treatment study. Your alternative is to not participate.

Introduction and Background Information

The study is being conducted under the direction of Dr. Jeffrey Travers, Principal Investigator. Dr. Craig Rohan is serving as a sub-investigator. The study visits and procedures will all occur at the Wright State Physician Health Center, Dermatology Clinic. The total number of subjects will be 40 or less. Candidates for this study include men and women who self-identify as having photosensitivity which is sensitivity to sunlight.

Sunlight exerts many effects on the body. We have evidence that in response to ultraviolet B radiation, which are the burning rays of sunlight, skin cells will release small pieces of themselves, known as microvesicle particles (MVP). Depending on one's skin type, these MVP's may be released earlier and in larger amounts after exposure to the sun, or later and in smaller amounts. Use of mouse studies make us think people with photosensitivity generate more MVP's due to Ultraviolet B (UVB) rays, than people without photosensitivity (which we will refer to as normal/control subjects).

Use of cell lines and mouse studies has shown that the drug imipramine can block MVP production from skin cells after UVB. We believe that the use of topical (applied to skin only) imipramine will block UVB-generated MVPs and decrease UVB-induced inflammation in both subjects with photosensitivity as well as in control ones.

The purpose of this consent form is to give you information about this research study. It will describe the purpose, procedures, benefits, risks, and discomforts of this study. Dr. Jeffrey Travers and the study staff will discuss this study with you and explain everything in detail. Please ask them to explain any words or information that you do not clearly understand.

It is up to you to decide whether or not to take part in this study. If you choose not to participate your decision will not affect your current or future relationship with Wright State Physicians. If you decide to participate, you are free to withdraw at any time without affecting that relationship. Please read this entire consent form and take your time to make your decision. We encourage you to talk to your doctor, your family, and/or your friends before you decide. Any questions that arise about the study will be answered by Dr. Jeffrey Travers at any point in time.

Who is conducting and funding this research study?

Wright State Physicians (WSP) Pharmacology Translational Unit will be conducting this trial under the direction of Dr. Jeffrey B. Travers, principal investigator. The study will be funded by the National Institute of Health.

Why is this research study being done?

The purpose of this study is to assess the effectiveness of the drug imipramine as a topical ointment in reducing microvesicle particle release after UVB exposure in subjects with photosensitivity. The use of imipramine in this study is considered investigational, meaning it has not been approved by the FDA for marketing in the United States for the use being testing in this research.

Why am I being asked to participate in this research study?

You have been chosen to participate in this study because you have self-identified as having photosensitivity or you do not.

How many people will be in this study?

Up to 40 subjects (20 with photosensitivity, 20 who do not) may be involved in this research at Wright State Physicians.

What will happen if I take part in this research study?

Your participation in this study will require 4 visits over 4 days.

Day 0: (6 hrs)

1. Following informed consent, follow-up appointments will be scheduled with the research team.
2. Subject photosensitivity questionnaire – this is a list of questions you will answer that include how you react to sunlight, and any conditions and medicines you are taking.
3. Volar (inner) forearm will undergo a mexameter reading which is an instrument that touches the skin to measure redness and brown color—this does not result in any pain. This test will tell us your exact skin type (white, brown, black).
4. Volar (inner) forearm skin will be photographed, and two 10 x 10 mm areas of skin (2/5th inch) area will undergo treatment with UVB irradiation blocked off with a 10 x 10 mm hole to allow UVB radiation to focus on the small area of skin.

The amounts we plan to use (1000 joules/meter^2) are similar to being out in direct sunlight approximately 2-3 hours in June/July in Bethesda MD (estimated from the UV-B Monitoring and Research Program of the United States Department of Agriculture (USDA) headquartered at Colorado State University; see http://uvb.nrel.colostate.edu/UVB/index.jsf).

5. On your back (same side as the forearm used) we will also deliver UVB in three 10 x 10 mm holes providing UVB levels of 0 J/m^2, 50 J/m^2, 100 J/m^2, 200 J/m^2, 400 J/m^2, 600 J/m^2, 800 J/m^2 with our portable UVB light unit (see Figure 1). This provides phototesting and acts as a control. We expect that this treatment will result in small areas of increasing amounts of redness by 24 hours, resulting in localized areas of mild sunburns.

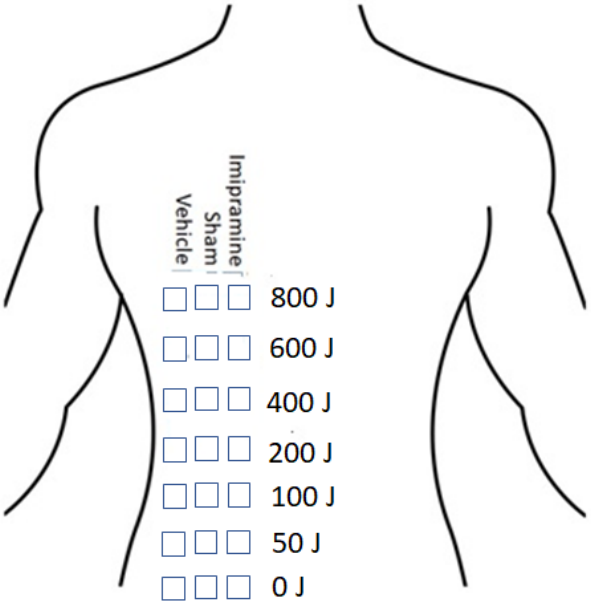

Figure 1

1. Treat back skin with various fluences of UVB and immediately add vehicle or 4% imipramine
2. 4 h later measure erythema with Mexameter
3. 24 h later measure erythema with Mexameter.

6. Immediately after UVB treatment, 2g of 4% imipramine or 2g of control vehicle will be added to both forearm and to back. On one area of UVB-treatment nothing will be added (sham). On the other forearm two areas 8 cm apart will be treated with imipramine or control without UVB.

7. You will return to clinic in 4 hours to allow us to remove the skin applications, and take pictures of the UVB-treated skin. We will also use a mexameter to

measure the redness of the UVB-treated areas on forearm and back. The two areas on the forearm treated with UVB + skin applications and two areas on the other forearm just treated with imipramine/vehicle will be photographed and 5 mm (1/5th inch) skin biopsies will be obtained from these four areas.

For the skin biopsies, the skin will be prepared in the usual sterile manner and anesthetized with 1% lidocaine with 1:100000 epinephrine. The lidocaine is a numbing medication and the epinephrine is used to decrease bleeding from the skin. The punch biopsy consists of cutting a round hole 5 mm across in the top layer of skin. If needed, a suture will be placed. The biopsies will be taken to our laboratory and placed into enzymes and MVP measured.

Please do not get the treated area on your back wet (no bathing/swimming, etc.) until you return to the clinic on Day 1.

Day 1: (30-60 minutes)
The next day, you will return to our clinic. The UVB-treated areas on the back will be photographed to document the redness response. We will again use a mexameter to measure redness.

Day 3: (30-60 minutes)
You will return to our clinic. The UVB-treated areas on the back will be photographed to document the redness response. We will again use a mexameter to measure redness.

Suture Removal. If sutures were placed for the skin biopsies, then you will be scheduled to have them removed 10-14 days after their placement. Wound care will be discussed and a sample of bacitracin ointment and bandaids supplied.

How long will I be in this research study?

If you choose to take part, you will be in the study for 4 days. If sutures are placed, you may be asked to return in 10-14 days for suture removal.

Can I stop being in this research study?

If you decide to participate, you are free to withdraw your consent and discontinue participation at any time without any penalty. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you

would otherwise be entitled. If you withdraw from the study, or the study medication is stopped for any reason, there is minimal risk of harm to you.

The principal investigator or study staff may also withdraw you from the study without your consent for one or more of the following reasons:

- Malfunction of study equipment (Mexameter).
- Failure to follow the instructions of the research study staff.
- You need treatment not allowed in the study.
- The study is cancelled.
- The principal investigator believes it is in your best interest.

What are the potential risks and discomforts from being in this research study?

Potential risks you may experience include:

1. UVB Treatment: Risks to the UVB protocol include an exaggerated response to UVB (sunburn). This in theory could result in a localized rash, pain and scarring. Our experiences thus far with using UVB at similar doses in other protocols has not resulted in any problems, which is to be expected given the doses (1000J/m^2) and small area (5 x 5 mm) of UVB irradiation. **Please note that our patients who are undergoing UVB treatments for their skin diseases (eg, psoriasis) end up getting much higher doses (>1000 J/m^2) over their entire body. Thus, these doses of UVB are likely quite safe.**
2. Imipramine: Topical use of imipramine is unlikely to cause any of the harmful effects/side effects listed with oral use. There is a risk of allergic reaction to imipramine, or other inactive ingredients in the ointment which is treatable.
3. Skin biopsies: Risk of allergic reaction to the local anesthetic lidocaine, risk of small scar at the biopsy sites, risk of wound infection at the biopsy sites, risk of bleeding from the biopsy site, risk of allergic reaction to suture material.
4. Photography: The risk of photography is the possible loss of confidentiality. Pictures will not be of recognizable body parts or markings. Photos will be labeled with the study number and a code that does not identify the subject. Photos will not include any identifying information.
5. Mexameter Readings: There is no risk to this non-invasive device.
6. There is also the potential risk of loss of confidentiality, but this will be minimized as photos of the wounded/UVB-treated sites will not allow the person to be identified, and will not expose buttocks or genitals. Samples will be labeled with numeric numbers --001, 002, 003 etc. and the study number (XXXXX). Example XXXXX-001.
7. In addition, you may experience harms that we have not included here.

Steps Taken to Reduce Risk of Coronavirus Infection

The following steps are being taken to address the risk of coronavirus infection:

Screening: If you show potential symptoms of COVID-19 (fever, cough, shortness of breath, etc.), you will NOT be permitted to participate in this study at this time. Our study team is required to show no potential symptoms of COVID-19 prior to reporting to work.

Physical distancing: Whenever possible, we will maintain at least 6 feet of distance from you while conducting the study.

Mask/Covering: You and our study team are required to wear a cloth face cover or mask that covers the mouth and nose during the study, even when maintaining at least 6 feet of distance. If you do not have a mask, one will be provided when entering the building. Tissues will be available to cover coughs and sneezes.

Handwashing: You and our study team will wash hands before/during examination or use a hand sanitizer.

Disinfecting materials: When feasible, we will clean and disinfect surfaces between participants, using an EPA-registered disinfectant for hard materials and by laundering soft materials. Disinfected materials will be handled using gloves, paper towel, plastic wrap or storage bags to reduce the chance of re-contamination of materials.

Electronics: Alcohol-based wipes or sprays will be used to disinfect shared touch screens, mice, keyboards, etc. Surfaces will be dried to avoid pooling of liquids.

Are there benefits to taking part in this research study?

You may not receive any personal benefit from being in the study. The information collected may not benefit you directly; however, the information may be helpful to others by providing us with an understanding of how sunlight and imipramine can have effects on the human body. This knowledge will help make it possible to provide the best type of treatment for patients in the future. While you may or may not personally benefit from being in this study, your participation will provide a benefit to others with this condition and to society.

What other options are there?

You have the option to not participate in this study. If you decide not to participate in this study, there is other care available to you, such as:

- Getting treatment or care without being in a study
- Taking part in another study
- Getting no treatment

The study doctor will discuss these with you.

What about privacy and confidentiality?

Total privacy cannot be guaranteed. We will protect your privacy to the extent permitted by law. If the results from this study are published, your name will not be made public. Once your information leaves our institution, we cannot promise that others will keep it private.

All conversations and procedures will take place in the Wright State Physician's building in the dermatology clinic in a private examining room. The data will be kept in the locked research office. Samples and pictures from subjects will be coded by numbers as outlined above. Photos will not be of recognizable body parts or markings.

Identifiers will be removed from your identifiable private information (or/and identifiable biospecimens). After such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without your (or your legally authorized representative's) consent.

FDA Clinical Trial Registry

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

What if I am injured as a result of my participation in the research study?

If you feel that you have been injured as a result of participating in the research, contact the research office or Dr. Travers at (937) 245-7500 to talk to them about your illness or injury.

If you are injured by being in this research study, you will be treated appropriately with no physician cost from Dr. Travers, though a pharmacy fee could be incurred if prescriptions are required. There are no plans for Dr. Travers or Wright State Physicians to provide other forms of compensation (such as lost wages or pain and suffering) to you for research related illnesses or injuries.

By signing this form you will not give up any legal rights.

What are the costs for participating in this research study?

There will be no costs to you for any of the procedures or testing done as part of this research study

Will I be reimbursed for any of my expenses or paid for my participation in this research?

You will be paid for participating in this study. You will be paid for each completed visit as follows:

Informed Consent- $20
Photosensitivity Questionnaire - $5
UVB treatment to arms and back- $30
Imipramine application - $5
Skin Biopsies - $25 each (Total - $100)
Return at Day 1 for redness readings and photography- $15
Return at Day 3 for redness readings and photography-$15
Completion of study- $35

Checks for the appropriate amounts will be provided to you after the end of the study day in person or mailed to the address provided.

If you complete all study visits, you will receive a maximum payment of $225. If you don't complete the study, you will be paid for the procedures you do complete.

Will I be told about new information that may affect my decision to participate in this research study?

During the course of the study, you will be informed of any significant new research information (either good or bad), such as changes in the risks or benefits resulting from participation in the research or new alternatives to participation, that might cause you to change your mind about continuing in the research. If new information is provided to you, you may be asked to sign a consent form that includes the new information.

Who should I contact if I have questions?

Contact the research office and Dr. Travers at (937) 245-7500 if you have any questions about this study or your part in it or if you have questions, concerns or complaints about the research.

If you have any questions about your rights as a research subject, you may call the Wright State University Institutional Review Board (IRB) at (937) 775-4462 or irb-rsp@wright.edu. The IRB is an independent committee composed of members of the University community, staff of the institutions, as well as lay members of the community not connected with these institutions. The IRB has reviewed this study.

What are my rights/responsibilities as a research subject?

As a subject, your responsibilities include:

- Follow the instructions of the research study staff.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the research study staff about any side effects that you may have.
- Tell the research staff if you believe you might be pregnant or have gotten your partner pregnant.
- Ask questions as you think of them.
- Tell the research staff if you change your mind about staying in the study.

While participating in this research study, you should not take part in any other research project without approval from the research staff of each study.

Authorization to Use and Disclose Your Health Information

State and Federal laws, including the Health Insurance Portability and Accountability Act (HIPAA), require researchers to protect the privacy of your health information. This section of the consent form describes how researchers, with your authorization (permission), may use and release (disclose or share) your protected health information (PHI) for this research study. **Please read this section of the consent form carefully.**

If you sign this document, you give permission to Dr. Travers and his Wright State Physicians Pharmacology Translational Unit research team to use or disclose (release) the following protected health information:

- Your medical records for past medical conditions and medications related to your skin conditions
- All information (research records and medical records) created during your participation in this research study

The research team needs this information to conduct the study. The purpose of this study is to assess the effectiveness of the drug imipramine as a topical treatment in reducing microvesicle particle release after UVB exposure in subjects with photosensitivity and others.

To maintain the integrity of this research, you might not have access to any health information developed as part of this study until it is completed. At that point, you generally would have access to your health information.

Disclosure of your protected health information

If you sign this form, the researchers may share your health information during the conduct of the study with:

- Non-Wright State Physicians researchers or organizations working with Wright State Physicians researchers.
- Law enforcement or other agencies, when required by law
- WSU's Institutional Review Board (or other IRB of record), which oversees our research
- The sponsor (the organization paying for) of this research study: National Institute of Health (NIH)
- Representatives of government agencies in the United States and other countries (i.e. Food and Drug Administration and the Office of Human Research Protection)
- Other authorized Wright State University/Physicians Officials who oversee research and clinical care

The people listed above will use and share your health information to review the quality, safety, and results of the research and may also do additional research.

Please understand that these persons/organizations who may receive your health information may not be required by U.S. Federal privacy laws (such as HIPAA) to protect it and may share your information with others without your permission.

This authorization does not have an expiration date.

However, you can change your mind and cancel this authorization at any time. To cancel this authorization, you must write the study investigator listed at the beginning of this consent form.

If you cancel this authorization, you will no longer be allowed to take part in the research study. If you cancel this authorization, health information you had already allowed us to obtain may still be used and disclosed by researchers in order to maintain the integrity and reliability of the research, and to report any adverse (bad) effects that may have happened to you.

Right to refuse to sign this Authorization

You have the right to refuse to sign and give your authorization. If you do not sign this form, your non-research related treatment, payment or enrollment in any health plans, or your eligibility for other medical benefits at Wright State Physicians will not be affected in any way.

However, if you do not sign this form, you will not be able to participate in this research study.

Signature of Subject

I have read (or someone has read to me) the above information. I have been given an opportunity to ask questions and my questions have been answered to my satisfaction. I agree to participate in this research and authorize the use and disclosure of my protected health information for this study. I will be given a copy of this signed and dated form.

_____
Signature

_____
Date

_____
Printed Name

_____
Signature of Person Obtaining Consent and Authorization

_____
Date

_____
Printed Name of Person Obtaining Consent and Authorization