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16-May-2022

INFORMED CONSENT AND RESEARCH AUTHORIZATION

Photodynamic Therapy and Microvesicles

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Staff Physician

Sponsor(s) name and address:
Wright State University Department of Pharmacology and Toxicology
3640 Col. Glenn Hwy
Dayton, OH 45435-0001

Site 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:
(937) 245-7500 or 775-2463

Key Information Summary

The purpose of this consent form is to give you information about this research study. It is up to you to decide whether 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.

The purpose of this study is to test if using 4% imipramine will block the increased levels of pieces of skin cells called microvesicle particles (MVP) produced from localized photodynamic therapy (PDT) treatment.

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

- Skin redness readings will be taken with a non-invasive mexameter. A mexameter is a noninvasive (does not break the skin) instrument that consists of a small probe that touches the skin to provide redness and pigmentary values.
- Two skin areas will be treated with 200mg of 10% 5-ALA gel (Ameluz).
- Photodynamic therapy treatment (blue light exposure) to the two skin areas then one site will be treated with 2g of 4% imipramine and the second area will be treated with 2 g of a base as control.
- Complete rating scales regarding skin pain and itch.
- Three 5mm punch biopsies (small hole in the top layer of skin) will be performed in a sterile manner to the anesthetized areas.

Your participation in this study last for 3 days.

Potential risks you may experience include:

- PDT treatment: PDT results in a localized sunburn-like reaction. The reactions can be associated with some itch and minimal pain.
- Skin biopsies: Risk of allergic reaction (rash, pain, itchiness) 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.

For the complete list of potential risks, please refer to the Potential Risk section starting on page 4.

You may not benefit by participating in this study. However, the information gain may be helpful to others.

The alternative to participating in this study is to not participate as this is not a treatment study.

Introduction and Background Information

You are invited to take part in this research study. This study does not involve any particular diagnosis. This study is only to obtain skin biopsy samples from male and female humans. The study is being conducted under the direction of Dr. Jeffrey Travers, Principal Investigator. The study procedures/visits will all occur at the Wright State Physician Health Center, Dermatology Clinic. The total number of subjects aged 18-45 will be 12 or less.

Purpose

This study is designed to test whether localized photodynamic therapy (PDT) will result in increased levels of microvesicle particles (MVPs; pieces of skin cells) and if the use of imipramine, a tricyclic antidepressant (TCA) medication that has been shown to interfere with the MVP production pathway, will counteract the release of these PDT generated MVP particles.

Introduction

Topical photodynamic therapy (PDT) consists of application of a gel, 5-aminolevulenic acid (5-ALA), to an area of skin followed by treatment with blue light. The treatment of this gel with blue light results in the production of molecules that lead to tissue destruction. Clinically, topical PDT is utilized as a noninvasive form of treatment for various skin cancers, such as basal cell carcinomas and premalignant actinic keratosis. Despite its use to treat pre-cancers and skin cancers, we have evidence that in response to the PDT, there will be release of microvesicle particles (MVPs; pieces of skin cells) that can communicate with the entire body and result in negative effects, such as inflammation and suppression of the immune system. These negative effects may result in a less effect PDT treatment for a patient.

We have evidence that MVP release can be blocked, thereby preventing its negative effects. One of these blocking agents for which we have evidence of effectiveness is imipramine, a tricyclic

antidepressant (TCA). A topical 4% imipramine would block the MVP production by inhibiting an important enzyme (sphingomyelinase) in the process.

Thus, we will test if PDT will make MVP in your skin and if 4% imipramine will result in a decrease in the MVP production. We will also measure redness of your skin and ask you to fill out a pain and itch scales (where you write how much itchiness or pain you have at site out of 10 as maximum). These will take place 4 hours after the PDT treatment and 2 days later when you return to the clinic.

Procedures

Your participation in this study will last for 3 days. If you consent to participate, you will receive the following procedures while you are in this study.

Day 0 (~8 hours)
Following informed consent, you will undergo the following procedures:

1. Two 2.5 x 2.5 cm areas of your dorsal (outer) forearm approximately 8 cm apart will be marked and the areas will be shaved with a razor to remove excess hair.

   Female subjects will provide a urine sample for a urine pregnancy test.

2. Baseline redness (erythema) readings will be taken using a non-invasive mexameter. A mexameter is a noninvasive instrument that consists of a small probe that touches the skin to provide redness and pigmentary values.

3. The two areas will be treated with 200mg of 10% 5-ALA gel (Ameluz) and will be covered with a large bandage dressing.

4. You will return **after 2 hours** and the bandages will be removed. Then, the areas will be treated with 10J of blue light (415 nm). This exposure will last 13.5 minutes, and during this time you will wear metal eye shields.

5. Immediately after the blue light exposure, one site will be treated with 2g of 4% imipramine and the second area will be treated with 2g of a base as control. These areas will then be covered with a non-adherent dressing.

6. You will return to the clinic **in 4 hours**. At that time, the imipramine and control will be removed from the PDT-treated sites. The mexameter will be used again to measure skin redness from the two areas and the areas will be photographed. We will ask you to fill out two pain and itch scales, where you rate each of the two areas from 0 (no pain/itch) to 10 (worse pain/itch you have ever experienced).

7. Next, the two treated skin areas and one area of normal skin on the inner surface of your opposite forearm will be 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. Three 5mm punch biopsies (small hole in the top layer of skin) will be performed in a

sterile manner to the anesthetized areas. If needed, a suture will be placed. The biopsies will be taken to our laboratory for the MVP measurement.

8. If sutures are placed, wound care will be discussed with you, and we will provide a sample of white petrolatum and bandaids. The Pharmacology Translational Unit staff will set up a visit in 10-14 days to have the sutures removed.

Day 2 (30 minutes)

1. 48 hours (2 days) after the treatments, we will ask you to return to clinic. We will photograph your arm and ask you to fill out Pain/itch questions rating each of the two sites from 0-10 as before.

Biospecimen Sampling for Research:

Research using biospecimens (saliva, blood, tissues, etc.) is an important way to try to understand human disease and functioning. There are several things you should know before allowing your biospecimens to be studied.

The type of specimens that will be stored and where they will be stored: Skin biopsies will be stored at Dr. Travers' laboratory on the Wright State University Campus.

Identifiability of Biospecimens: The samples will be coded by study number XXXXX followed by subject number 001, 002, 003, etc.

The length of time your biospecimen will be stored until they are destroyed: Your samples will be stored until the analyses are completed. At that time, they will be destroyed.

How to withdraw your biospecimens from the study:
Because your samples will not be linked to your name after they are stored, you cannot withdraw your consent to the use of the samples after they are taken.

Future Use of Biospecimens:

Information or specimens for this research may be used for future research studies or shared with other researchers for future research. If this happens, any information which could identify you will be removed before any information or specimens are shared. Since identifying information will be removed, we cannot ask for your additional consent.

The biospecimens will be used for the following types of analyses/studies: Your samples will be used to study other proteins/genes in the skin that could indicate skin damage and/or effects of PDT on skin.

When results will be given to you: The results of your samples will be used for research purposes only and you will not be told the results of the test.

Potential Risks

1. PDT treatment: PDT results in a localized sunburn-like reaction. The reactions can be associated with some itch and minimal pain. It is possible that you could experience a severe reaction, to include blistering. If you are in significant pain or severe skin itch, Dr. Travers, a Board-Certified Dermatologist, will provide a free tube of topical corticosteroid triamcinolone cream to treat. An example of this procedure is found in Figure 1.

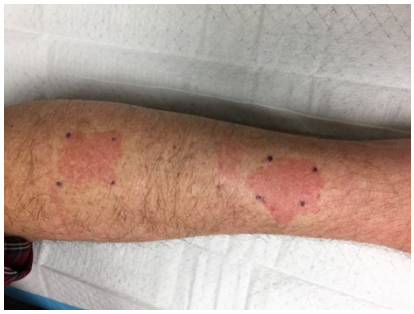

Figure 1.
Example of reactions following PDT

2. Skin biopsies: Risk of allergic reaction (rash, pain, itchiness) 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. The wound infection rate is approximately 4%—thus we will give standard wound care instructions and samples of Vaseline ointment. Risks of poor wound healing or abnormal scarring will be assessed as subjects will be asked about previous history of abnormal scars, or systemic diseases such as diabetes mellitus which could predispose them to poor wound healing/increased incidence of skin infections. Risks of wound infection and scarring from the skin biopsies will be minimized as Dr. Travers has 20+ years of experience in these procedures.

3. Topical imipramine: Topical imipramine is used clinically. It is possible that a subject could be allergic to imipramine. If that happens, it would cause an itchy rash.

4. Topical 5-aminolevulinic acid gel (Ameluz): This agent and the blue light is the PDT. This chemical on your skin can cause increased reactions to sunlight (sun burn), so we ask you to avoid direct sunlight (more than 5 to 10 minutes outside with arm uncovered by clothes) or other light such as tanning beds to the treated areas for at least 3 days. We ask that you use sunscreen and cover with long sleeves for the next three days after the PDT treatment.

5. There are no risks to photography nor mexameter readings. Photographs will not allow the subject to be recognizable.

6. There is also the potential risk of loss of confidentiality, but this will be minimized, as samples will be labeled with numbers. The Study number XXXX followed by 001, 002, 003 etc.

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.

Benefits

There may not be a direct benefit to you by participating in this study. Despite this, the information acquired through this research may be helpful to others by providing us with an understanding of how PDT impacts the human body and how any of its negative effects can be minimized.

Alternatives

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

Compensation & Treatment for Injury

You will be compensated for involvement in the study. If you complete all study components, you will receive a maximum compensation value of $200. There is no cost for parking at the Wright State Physician's Building. Compensation is based upon completed study visit and overall study completion; you will be compensated even if you are unable to complete all components of the study. Per visit compensation values are broken down as follows:

Informed Consent - $20
PDT treatment- $30
Topical applications- $20
Skin Biopsies- $25 each (Total - $75)
Return at Day 2 (48h) for redness readings and photography- $25

Completion of Skin Pain and Itch Scales - $5 (Total - $10)
Completion of study- $20

Total Compensation: **$200**

Checks for the appropriate amount will be provided to you at the end of the study day either in person or mailed to the address provided.

If being in this research study results in injury to you, the investigator will arrange for you to get medical treatment from Dr. Travers. As mentioned in the discussion of potential risks, an unlikely but possible adverse reaction would be a biopsy site infection. This would manifest as increased pain and pus in the biopsy site approximately 4-7 days after the procedure. If this occurs, Dr. Travers will provide you with a tube of prescription antibiotic mupirocin ointment. If ineffective, Dr. Travers will prescribe an oral antibiotic, for which the cost would need to be covered by you or your insurance company. If you are injured, there is no money set aside for lost wages, discomfort, disability, etc. You do not give up your legal rights by signing this form. If you think you have an injury related to this research, please call the PI or research office at (937) 245-7500 or (937) 775-2463. If an adverse event occurs, please contact Dr. Travers who will provide treatment as outlined above.

Research Subject Costs

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

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.

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.

Data Security

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 office of the PI. Samples and pictures from subjects will be coded by numbers as outlined above. Photos will not be of recognizable body parts or markings.

Voluntary Participation

Taking part in this study is completely voluntary. You may choose not to take part. If you decide not to be in this study, you will not be penalized or lose any benefits for which you qualify. If you decide to be in this study, you may change your mind and stop taking part at any time. If you decide to stop taking part, you won't be penalized or lose any benefits for which you qualify. You will be told about any new information learned during the study that could affect your decision to continue in the study.

Termination

The investigator, the IRB or the study sponsor has the right to stop this study at any point. The investigator may take you out of this study with or without your permission. An example of why this may occur includes: malfunction of study equipment such as the Mexameter.

Your 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, doctor visits, or hospitalizations that you may have.
- Tell the research staff if you believe you might be pregnant.
- Ask questions as you think of them.
- Tell the research staff if you change your mind about staying in the study.

You may take part in this study if you are currently in another research study. It is important to let the investigator know if you are in another research study.

Research Subject's Rights, Questions, Concerns, and Complaints

If you have any questions, concerns, or complaints about the research study you may contact the principal investigator, Dr. Travers, or research office at (937) 775-2463 or (937) 245-7500.

If you have any questions about your rights as a study subject, questions, concerns or complaints, you may call the Wright State University Institutional Review Board (IRB) at (937) 775-4462 or irb-rsp@wright.edu. You may discuss any questions about your rights as a subject with a member of the

IRB or staff. 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.

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. This is a study to test if using 4% imipramine will block the increased levels of pieces of skin cells called microvesicle particles (MVP) produced from localized photodynamic therapy (PDT) treatment.

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