2000025289

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH STUDY

YALE UNIVERSITY
YALE UNIVERSITY SCHOOL OF MEDICINE
YALE-NEW HAVEN HOSPITAL

Study Title: Inhibition of Sterile Inflammation by Digoxin
Principal Investigator (the person who is responsible for this research):

Wajahat Mehal, PHD, MD
Department of Internal Medicine, Section of digestive diseases
TAC building
1 Gilbert street
New Haven, CT 06519

Phone Number: 203-606-5140

Why is this study being offered to me?

You are invited to participate in this research study designed to test whether administration of oral digoxin to healthy subjects results in a reduction in innate immune inflammatory responses in the peripheral blood. Digoxin is a medication known as a cardiac glycoside, and is typically used to treat various heart conditions. If digoxin is shown to reduce inflammatory responses, it could possibly play a role in the treatment of liver diseases such as alcoholic hepatitis (AH), of which inflammation is a key feature. You have been asked to participate because we are looking for healthy subjects for this study and you are eligible for this participation. We expect that 45 subjects will take part of this study here at Yale University.

To decide if you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion will go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Study procedures will include:

You will be asked to take oral digoxin once daily for 21 days. There are four (4) clinic visits within 28 days which will last approximately about half an hour per visit). The visits will take place at the Yale Center for Clinical Investigation, 2nd church street, New Haven, USA, 06519. To demonstrate that oral digoxin can reduce inflammatory markers in human blood, and to obtain an initial idea of digoxin dosages required for this we will conduct a dose response of oral

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digoxin in healthy individuals. The highest digoxin dose will be at the lower end of the currently recommended dosing range for digoxin, 3 mcg/kg/day, and we will test a lower dose, 0.15 mcg/kg/day, as well. A placebo (sugarless syrup) group will serve as a control. Serum digoxin levels and EKG's will be assayed weekly (four clinical visits). We will ask you about any side effects that you may be experiencing, regardless of your digoxin levels. The study doctor might ask you to stop taking the drug if any serum digoxin level is above 0.8ng/ml, or if there are any abnormalities in blood tests or EKGs.

While you will not benefit from your participation in this study, the knowledge gained from this study may be beneficial to patients with alcoholic hepatitis in the future.

Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You can also change your mind at any time. Whatever choice you make; you will not lose access to your medical care or give up any legal rights or benefits.

If you are interested in learning more about the study, please continue reading, or have someone read to you, the rest of this document. Take as much time as you need before you make your decision. Ask the study staff questions about anything you do not understand. Once you understand the study, we will ask you if you wish to participate; if so, you will have to sign this form.

Who is paying for the study?

This study is funded by a grant for the National Institutes of Health.

Who is providing other support for the study?

The phlebotomy, EKG and handing the medication will take a place in Yale Center for Clinical Investigation (YCCI)

What is the study about?

The purpose of this study is to assess the degree of inflammatory markers decline in healthy individuals. Digoxin is an FDA approved drug which is used in adults for the treatment of mild to moderate heart failure and for controlling the heart rate in patients with an abnormal rhythm called atrial fibrillation. We are using digoxin in this study because it may have strong anti-inflammatory properties. We'll be separating out different kinds of white blood cells and evaluating their responses to things that normally trigger inflammation. We think that digoxin will suppress the cells' inflammatory responses.

What are you asking me to do and how long will it take?

If you agree to take part in this study, this is what will happen:

Screening:

On the initial visit, you will be asked to provide your clinical history, undergo a physical exam, have a pregnancy test if you are a female of childbearing potential, and a baseline screening to determine if you are eligible for this study. The baseline screening includes collection of blood specimens for a complete blood count and chemistry panel, collection of a urine sample if needed, and an electrocardiogram, which is a procedure that monitors the activity of your heart by placing electrodes on your chest and body. This is also known as an EKG.

You will be given oral digoxin (3 mcg/kg/day or 0.15 mcg/kg/day) or placebo to take daily for 21 days to take at home.

If you are eligible for the study, you will be advised not to take any over the counter medications, prescription medications or natural products during this study period.

Your will be randomized (by a computer) to one of the following groups:

Group A: Placebo
Group B: 3 mcg/Kg/day
Group C: 0.15mcg/Kg/day

Digoxin is commercially available as a 0.05mg/ml elixir (Boehringer Ingelheim). The digoxin and placebo control will be prepared and stored by the department of pharmacy services in YNHH.

Schedule of Activites:

First visit: Baseline EKG and a baseline blood sample (18 ml / 1.2 tablespoons). Your weekly dose of study medication will be given as an elixir in a bottle with a dropper. Drops should be put directly to the mouth.

Second visit (after 7 days): EKG and a blood sample (18 ml / 1.2 tablespoons). Your weekly dose of study medication will be given as an elixir in a bottle with a dropper.

Third Visit (after 7 days): EKG and a blood sample (18 ml / 1.2 tablespoons). Your weekly dose of study medication will be given as an elixir in a bottle with a dropper.

Fourth Visit after (7 days): EKG and a blood sample (18 ml / 1.2 tablespoons). Study terminates.

Method: You should put the drops directly in your mouth`

Food to Avoid: Dietary fiber, specifically insoluble fiber such as wheat bran, can slow down the absorption of digoxin and lessen its effectiveness. To prevent this, participants should take digoxin at least one hour before after eating a meal.

Herb use can also affect digoxin. For example, ginseng can elevate blood levels of digoxin by as much as 75%, while St. John's Wort decreases blood levels of this drug by 25%.

In the event that you experience a serious adverse event related to the digoxin, you will be removed from study and medical care will be provided at Yale New Haven Hospital if needed. This is an investigational study and all the subjects will undergo the same procedures regardless of which group they are assigned to.

You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate.

What are the risks and discomforts of participating?

The following risks are associated with participating in the study:

- Adverse effects from digoxin and its toxicity (e.g. Dizziness, Changes in mood and mental alertness, including confusion, depression and lost interest in usual activities, Anxiety, Nausea, vomiting and diarrhea, Headache)
- Subjects will be removed from study and medical care will be provided at Yale new haven hospital if needed.
- Allergic reaction to digoxin.
- Risks and discomforts of phlebotomy.
- Risks and Inconveniences of an electro-cardiogram (EKG.
- Risk to a pregnancy/fetus.
- Breach of confidentiality.

Withdrawing from the study: If you wish to discontinue from the study, for any reason, the intervention will be immediately terminated and consent to participate may be rescinded at your discretion.

Pregnancy Risks:

- It is not known if the study drug (digoxin) can cause harm to a fetus or have an effect on reproductive capacity (i.e., the number of children you can have). Therefore, it is important that you do not participate if you are pregnant or think you might become pregnant.

- During your participation, you should be on an effective form of contraception.

- The drug may be present in the breast milk, although the amount is small and should not have any effect upon a nursing infant.

How will I know about new risks or important information about the study?

We will tell you if we learn any new information that could change your mind about taking part in this study.

How can the study possibly benefit me?

This study is not designed to benefit you.

How can the study possibly benefit other people?

This study may generate clinical data supporting the anti-inflammatory use of digoxin in various conditions including alcoholic hepatitis and may benefit science by answering a scientific question. The question it will answer is whether taking digoxin orally can modulate the immune response of peripheral blood lymphocytes.

Are there any costs to participation?

You will not have to pay for taking part in this study. The digoxin, blood tests and EKGs will be provided at no cost to you. The only costs include transportation and your time coming to the study visits.

Will I be paid for participation?

You will be compensated $75 for each of the study visits, for a total of $300 ($75x4) if you complete all four visits required by the study. You will be provided parking passes at each visit to cover parking if you park in the ProPark lot surrounding the building.

According to the rules of the Internal Revenue Service (IRS), payments that are made to you as a result of your participation in a study may be considered taxable income. The payment is not conditional on completing the study, you will be compensated on weekly basis.

What are my choices if I decide not to take part in this study?

Your alternative to participating in this study is not to participate.

How will you keep my data safe and private?

We will keep information we collect about you confidential. We will share it with others if you agree to it or when we have to do it because U.S. or State law requires it. For example, we will tell somebody if you we learn that you are hurting a child or an older person.

Paper forms will be kept in each study participant's record and will be stored in a locked file cabinet in PI office at 1 Gilbert Street TAC building, room S223A. Only the PI and study staff will

have access to the participant's records. Forms will be coded with subject number; no personally identifiable information will be associated with these forms.

When we publish the results of the research or talk about it in conferences, we will not use your name. If we want to use your name, we would ask you for your permission.

We will also share information about you with other researchers for future research, but we will not use your name or other identifiers. We will not ask you for any additional permission.

What Information Will You Collect About Me in this Study?

We will be collecting basic demographic data on you (Name, date of birth, gender, weight and height (to calculate BMI)), additional information that will help us communicate with you like (telephone number(s), mailing address, email address) and your personal history with (medications, other diagnoses). Only the investigators will have access to PHI.

The information we are asking to use and share is called "Protected Health Information." It is protected by a federal law called the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). In general, we cannot use or share your health information for research without your permission. If you want, we can give you more information about the Privacy Rule. Also, if you have any questions about the Privacy Rule and your rights, you can speak to Yale Privacy Officer at 203-432-5919.

The specific information about you and your health that we will collect, use, and share includes:

- Research study records
- Medical and laboratory records of only those services provided in connection with this Study.
- The entire research record and any medical records held by Yale University created from: July 1st 2019 to April 4th 2024.
- Records about phone calls made as part of this research
- Records about your study visits
- Study Doctor will scan your record for:
    - HIV / AIDS test results
    - Hepatitis infection
    - Sexually transmitted diseases
    - Other reportable infectious diseases
    - Physical exams
    - Laboratory, x-ray, and other test results
    - Diaries and questionnaires
    - The diagnosis and treatment of a mental health condition
    - Use of illegal drugs or the study of illegal behavior
    - Records about any study drug you received

- Research study records

- Medical and laboratory records of only those services provided in connection with this Study.
- The entire research record and any medical records held by Yale university created from: 04-04-2019 to04-04-2024

How will you use and share my information?

We will use your information to conduct the study described in this consent form.
We may share your information with:

- The U.S. Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University, the Yale Human Research Protection Program and the Institutional Review Board (the committee that reviews, approves, and monitors research on human participants), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- The U.S. Food and Drug Administration (FDA) This is done so that the FDA can review information about Digoxin involved in this research. The information may also be used to meet the reporting requirements of drug regulatory agencies.
- The study sponsor or manufacturer of study drug/device
- Drug regulatory agencies in other countries
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- Health care providers who provide services to you in connection with this study.
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- Co-Investigators and other investigators
- Study Coordinator and Members of the Research Team
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study

We will do our best to make sure your information stays private. But, if we share information with people who do not have to follow the Privacy Rule, your information will no longer be protected by the Privacy Rule. Let us know if you have questions about this. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

Why must I sign this document?

By signing this form, you will allow researchers to use and disclose your information described above for this research study. This is to ensure that the information related to this research is available to all parties who may need it for research purposes. You always have the right to review and copy your health information in your medical record.

However, this is a single/double blinded treatment study and if you sign this permission form, you will not be allowed to look at or copy your study related information until after the research is completed.

What if I change my mind?

The authorization to use and disclose your health information collected during your participation in this study will never expire. However, you may withdraw or take away your permission at any time. You may withdraw your permission by telling the study staff or by writing to

Wajahat Mehal, PHD, MD
Department of Internal Medicine, Section of digestive diseases
TAC building
1 Gilbert street
New Haven, CT 06519 at the Yale University, New Haven, CT 06520.

If you withdraw your permission, you will not be able to stay in this study but the care you get from your doctor outside this study will not change. No new health information identifying you will be gathered after the date you withdraw. Information that has already been collected may still be used and given to others until the end of the research study to insure the integrity of the study and/or study oversight.

Who will pay for treatment if I am injured or become ill due to participation in the study?

If you are injured while on study, seek treatment and contact the study doctor Wajahat Mehal 203-606-5140, 203-785-3411, 203-737-6063 as soon as possible. The Study PI and Yale School of Medicine will not provide funds for the treatment of research-related injury; if necessary, the PI will identify the appropriate medical treatment in conjunction with the patients' clinicians. The PI and Yale School of Medicine are not obliged to pay for any such treatment. You do not give up any of your legal rights by signing this form.

What if I want to refuse or end participation before the study is over?

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

You can withdraw from this study at any time without providing explanation. To withdraw from the study, you can call a member of the research team at any time and tell them that you are no longer wanting to take part. This will cancel any future appointments.
The researchers may withdraw you from participating in the research if necessary (e.g., development of serious side effects or toxicity to digoxin, or subject's non-compliance). In addition, if you start taking any over the counter drugs, prescription medication, and natural products during the study period, you will be removed from study.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with Yale-New Haven Hospital.

Study doctor might decide you should stop taking the drug if any serum digoxin level is above 0.8ng/ml, or if there are any abnormalities in blood tests or EKGs. Data from these subjects will not be used in the analysis

What will happen with my data if I stop participating?

When you withdraw from the study, We will not collect any additional data. Data already collected will be deidentified and used in data analysis as necessary to insure the integrity of the study and/or study oversight.

We will store it in a private secure place until 04-04-2024.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the National Institute of Health which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of reports of child abuse and neglect, or harm to self or others or communicable diseases.

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document.

Who should I contact if I have questions?

Please feel free to ask about anything you don't understand.

If you have questions later or if you have a research-related problem, you can call the Principal Investigator (Wajahat Mehal) t 203-606-5140

If you have questions about your rights as a research participant, or you have complaints about this research, you call the Yale Institutional Review Boards at (203) 785-4688 or email hrpp@yale.edu.

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

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Authorization and Permission

Your signature below indicates that you have read this consent document and that you agree to be in this study.

We will give you a copy of this form.

Participant Printed Name	Participant Signature	Date

Person Obtaining Consent Printed Name	Person Obtaining Consent Signature	Date

Complete if the participant is not fluent in English and an interpreter was used to obtain consent. Participants who do not read or understand English must not sign this full consent form, but instead sign the short form translated into their native language. This form should be signed by the investigator and interpreter only. If the interpreter is affiliated with the study team, the signature of an impartial witness is also required.

Print name of interpreter: _____

Signature of interpreter: _____ Date: _____

An oral translation of this document was administered to the participant in _____ (state language) by an individual proficient in English and _____ (state language).

Print name of impartial witness: _____

Signature of impartial witness: _____Date: _____

See the attached short form for documentation.

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