Mirabegron and Physiological Function in Cold Environments

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INDIANA UNIVERSITY INFORMED CONSENT STATEMENT FOR RESEARCH
Mirabegron and Physiological Function in Cold Environments
Mirabegron and Thermogenesis in Cold Air - Funded by the Office of Naval Research

ABOUT THIS RESEARCH
You are being asked to participate in a research study. Scientists do research to answer important questions which might help change or improve the way we do things in the future.

This consent form will give you information about the study to help you decide whether you want to participate. Please read this form, and ask any questions you have, before agreeing to be in the study.

TAKING PART IN THIS STUDY IS VOLUNTARY
You may choose not to take part in the study or may choose to leave the study at any time. Deciding not to participate, or deciding to leave the study later, will not affect your grades or result in any penalty or loss of benefits to which you are entitled, and will not affect your relationship with the Indiana University – Bloomington School of Public Health, or the Human Performance Laboratories.

Study Summary
Navy Divers often perform work in cold water. However, their protective equipment is cumbersome and does not completely prevent decreases in body temperature during cold water dives. Thus, alternative solutions that keep divers warm during cold water exposure are needed to improve diver safety.

Mirabegron is an FDA approved drug for the treatment of overactive bladder. Mirabegron also increases body temperature and therefore might be an alternative strategy that can improve cold water tolerance in divers. However, before we examine the effects of mirabegron during cold water immersion we need to know which dose of mirabegron increases body temperature the most. Therefore, the purpose of this study is to determine which dose of mirabegron can elevate body temperature the most during mild cold air exposure.

You will be asked to come to the laboratory for five visits (~33 total hours); one screening visit (~1 hour) and 4 study visits (~8 hours each). During the screening visit we will determine your eligibility, resting blood pressure and heart rate, and determine your body composition. During the 4 study visits, you will ingest a single dose of mirabegron or a placebo (a sugar pill) and spend 6 hours in a room that is mildly cold. We will measure your body temperature, heart rate, blood pressure, and shivering during the study. We don't expect you to receive any benefit from taking part in this study, but we hope to learn things which will help scientists in the future. Taking part in this research may expose you to risks. These risks include tearing of the rectum, infection, and feeling cold. We will attempt to minimize these risks by having all procedures performed by trained individuals and through monitoring of your condition during the study. Payment for your time is available if you decide to take part in this study. There is no cost to you for taking part in this study.

Please review the rest of this document for more details about this study and the things you should know before making a decision about whether to participate in this study.

WHY IS THIS STUDY BEING DONE?

Navy and Special Warfare Divers are often exposed to cold water during their missions. Although these divers wear thermal protection, it is often cumbersome and does not completely protect the diver from the cold. This can affect the diver's performance and safety while trying to carry out their tasks. Therefore, new strategies are needed to improve tolerance to cold water. Mirabegron is an FDA-approved drug for the treatment of overactive bladder. Mirabegron also raises body temperature. Therefore, divers could ingest mirabegron prior to a cold water dive in order to increase their body temperature and improve cold water tolerance. However, we don't know what dose of mirabegron can increase body temperature for extended periods of time. Therefore, the purpose of this study is to determine which dose of mirabegron can elevate body temperature the most during mild cold air exposure.

You were selected as a possible participant because you are 18-40 years of age and generally healthy.

The study is being conducted by Dr. Blair Johnson and the Indiana University – Bloomington, Department of Kinesiology within the School of Public Health. It is funded by a grant from the Office of Naval Research.

HOW MANY PEOPLE WILL TAKE PART?

If you agree to participate, you will be one of 30 participants taking part in this research.

WHAT WILL HAPPEN DURING THE STUDY?

If you agree to be in the study, you will do the following things:

- You will be asked to visit the Human Performance Laboratories at the School of Public Health Building at 1025 E. 7th Street, Room 075, Bloomington, IN 47405. Parking is free in designated parking spots behind the building or in the parking lot out front.
- For these visits you will be asked to wear comfortable clothing during the visit at the laboratory (men: no shirt and shorts; women: sports bra and shorts) (visits 2-5).
- We expect that you will be in this research study for about 33 hours over a total of five visits. The first visit will be used for informed consent (about 1 hour) and the remaining four visits will be used for the study visits (about 8 hours each). Each study visit will be separated by at least 10 days. If you are determined not to be eligible based on screening, you will be withdrawn after the first visit. Please consider your schedule and any classes or meetings that may be affected by the strict time requirements for this study.

This is a brief description of what will happen on each study visit. There are further details below this section explaining each study procedure as well as the risks associated with that procedure.

- **Screening / Visit 1**: Once you arrive at the laboratory, an investigator will get written informed consent after all procedures and study risks are fully explained and all questions answered. After

obtaining written informed consent, you will complete a Health History and Demographics Questionnaire, an International Physical Activity Questionnaire (IPAQ), and a Physical Activity Readiness Questionnaire (PAR-Q+). An experienced investigator will administer these questionnaires and they can fully explain any technical terms and answer any inquiries related to the questionnaires. Your blood pressure and heart rate will be measured. You will meet with our study physician to determine if you should not take mirabegron or participate in the study. You will be taught how to use the myfitnesspal dietary log (myfitnesspal.com or mobile app). Prior to each remaining study visit, you will show the study staff your food and fluid intake for the 3 days before your study visit. You will also have your height and weight measured and your body composition will be assessed (dual-energy X-ray absorptiometry (DEXA)). During the DEXA scan, you will lay on your back for approximately 10 minutes while the scanner images your body to determine your body composition. If you cannot see our physician or perform the body composition assessment during this visit, additional visits can be scheduled. You can also visit with the study physician over a Zoom call to review your medical history. The total time for this screening visit will take approximately 1 hour.

- **Visits 2-5**: You will be asked to complete 4 visits that will take approximately 8 hours each to complete. For 3 days prior to each study visit, you will be asked to record the amount and type of food and fluid that you consume using myfitnesspal dietary log. This free program is available at the website (myfitnesspal.com) or as an app for your mobile device. We ask that you consume the same amount and type of food and fluid for 3 days prior to each visit because your diet might influence the results of your study. We will view your dietary log to make sure that you consume the same type and amount of food and fluid prior to each visit. You will be asked to report to the laboratory in the morning after no exercise, caffeine, and alcohol for 24 hours, and no food for 12 hours. You will also be asked to not take any medication the day of these visits (except birth control). Men will be asked to be shirtless and wear shorts and women will be asked to wear a sports bra and shorts during these visits.

- These 4 visits will only differ by the amount of mirabegron or placebo that you will ingest. The order of these visits will be randomly determined (by chance, like rolling a die).
    - Placebo
    - 100 mg mirabegron
    - 150 mg mirabegron
    - 200 mg mirabegron

- Upon arrival at the laboratory, you will complete a Health History Update Questionnaire to ensure no relevant changes in your health history have occurred. Women of child-bearing potential will give a urine sample that will be used for a urine pregnancy test. The remaining urine may be stored for later analyses. You will consume a light breakfast (237 ml (8 fluid oz) of Ensure Original; 220 kcal). You will then self-insert a rectal probe that will be used to measure your internal body temperature.

- We will attach equipment to monitor you over the course of the study. There will be various tests that are described in detail below under “Experimental Procedures”.

- After 20 minutes of quiet resting, a baseline set of recordings will be started and a small amount of blood (approximately 3 teaspoons or 15 mL) will be taken from a vein in your arm before you ingest the mirabegron or placebo

- We will then have you ingest the mirabegron or placebo and 30 minutes following ingestion, you will enter the whole-body indirect calorimeter room. This room is designed to comfortably measure your energy expenditure by collecting the air you breathe out over a long period of time. The temperature of the room will be set to 68°F (20°C).

- You will spend 6 hours in the whole-body indirect calorimeter room. During the 6 hours, you will be free to watch television or read. We will ask that you perform the same amount of television watching and reading between study visits. For instance, if you watch television for 3 hours during one visit, you will be asked to watch television for 3 hours during subsequent visits.

- Every 30 minutes we will record your body temperature, heart rate, and blood pressure.

- Every 60 minutes you will be asked to lay down and rest for 30 minutes as we record your energy expenditure.

- You will be given the opportunity to use the restroom after approximately 3 hours in the chamber and urine will be collected at this time.

- At the end of the 6 hour protocol, you will exit the whole-body indirect calorimeter and we will record your body temperature, heart rate, and blood pressure and a small amount of blood (approximately 3 teaspoons or 15 mL) from a vein in your arm. After this we will give you a blanket to warm yourself if you choose.

- Prior to leaving the laboratory, we will provide you with a fecal (stool) collection kit. We will give you verbal and written instructions on how to obtain a small fecal sample (less than 1 teaspoon or 0.5 mL) from your first bowel movement following the study visit. We will provide you with shipping instructions or you can bring the sample back to the laboratory and a staff member will ship the sample for analysis.

Experimental Procedures: The procedures listed below are designed for research and are not for medical purposes.

Mirabegron:

Description: You will ingest mirabegron tablets with a small glass of water. The dose of mirabegron, 100 mg, 150 mg, and 200 mg will be randomly selected for each study visit.

Potential Risks: There are risks associated with ingesting mirabegron such as, increased blood pressure and heart rate, nasopharyngitis (common cold), urinary tract infection, urinary retention, angioedema (swelling in the skin or lips), headache, constipation, upper respiratory tract infection, arthralgia (joint pain), diarrhea, abdominal pain, and fatigue.

Duration: Once for each study visit.

DEXA Scan:

Description: You will lay on your back while the scanner images your body to determine your body composition.

Potential Risks: If you have had radiation (like x-rays, CT or radiation therapy) before or you participated in a different study where you were exposed to radiation, please tell us now. We want to make certain that the probability of harm from the amount of radiation you will be exposed to in this study continues to be low when combined with the radiation you have received within the past year. If you are pregnant, you cannot take part in this research study. If you are able to have a baby, are not pregnant and wish to take part in this study, you will need to take a pregnancy test prior to enrollment. If you get pregnant while taking part in this study, or think you are pregnant, please tell the research team right away. You will not be able to continue this study if you become pregnant.

The DEXA scan that you get in this study will expose you to low amounts of radiation. Every day, people are exposed to low levels of radiation that come from the natural environment and man-made radiation sources around them. This type of radiation is called "background radiation." The amount of radiation you will get from the scans in this study is approximately, or less than, 1 years' worth of background radiation. The probability of harm from participating in this study is low compared to other everyday risks. Certain diseases or conditions may affect your sensitivity to radiation. For more detailed information on the risks of radiation or if you wish to have a more detailed dose estimate, please ask the research team involved with this study.

For women of child-bearing potential: This study may be hazardous to an unborn child. The amount of radiation exposure necessary to present a significant risk to an unborn child is not well established; however, recommendations exist which limit the exposure to the unborn child of individuals who are occupationally exposed to radiation (e.g. x-ray technologists, radiologists, etc.) to no more than 500 millirem (mrem). Should you be pregnant and participate in this study, the radiation dose to the unborn child would be less than 500 mrem; however, pregnant individuals should not participate in this study. To assure that you are not pregnant, a pregnancy test will be performed at no cost to you, prior to initiation of the study. The results of the pregnancy test will be made available to you before the study is initiated. Furthermore, adequate birth control measures should be taken during your participation in this study.

Duration: Once, for approximately 5-10 minutes during Visit 1.

Electrocardiogram (measure of the electrical output of your heart):
Description: Sticky patches will be applied to your skin to measure heart rate from your heart's electrical signals.
Potential Risks: There may be some discomfort from removing the tape.
Duration: During all visits except Visit 1, continually measured.

Skin Temperature:
Description: Sticky patches will be applied to your skin to measure your skin temperature.
Potential Risks: There may be some discomfort and/or redness from removing the tape.
Duration: During all visits except Visit 1, continually measured.

Arm Blood Pressure:
Description: Your blood pressure and heart rate will be monitored using a cuff placed on your upper arm that is inflated and deflated periodically.
Potential Risks: You may feel slightly uncomfortable due to inflation of the cuff around your arm, but there are no risks.
Duration: The cuff will be on your upper arm during all visits. Blood pressure measurements will be taken at several different time points. Each measurement will last approximately 30 seconds.

Infrared Thermography Images:
Description: We will take pictures of your upper body to measure skin temperature near your collar bone.
Potential Risks: None.
Duration: During all visits except Visit 1, every 30 minutes.

Surface Mechanomyography (shivering):
Description: We will adhere triaxial accelerometers, similar to a watch, to your chest, upper back, and thigh using tape.
Potential Risks: There may be some discomfort from removing the tape.
Duration: During all visits except Visit 1, continually measured.

Bedside Shivering Scale:
Description: Two investigators will rate how much you are shivering.
Potential Risks: None.
Duration: During all visits except Visit 1, every 30 minutes.

Perceptual Scales (questionnaires):
Description: You will be shown standardized scales to rate your whole-body thermal sensation 1 ("cold") to 7 ("hot") and thermal comfort 1 ("comfortable") to 4 ("very uncomfortable")
Potential Risks: None.
Duration: During all visits except Visit 1, every 30 minutes.

Energy Expenditure (thermogenesis):
Description: The air you breathe out will be used to calculate energy expenditure.
Potential Risks: None.
Duration: During all visits except Visit 1, every 60 minutes.

Urine Sample:
Description: You will provide urine samples in a private bathroom that will be tested for pregnancy status (women of childbearing potential only) and urine specific gravity for both men and women.
Potential Risks: None.
Duration: During all visits except Visit 1, before we attach you to our monitoring devices, after ~3 hours in the chamber, and at the end of each study visit.

Body Height and Weight:
Description: You will be asked to measure your height and weight without clothes on using a stadiometer (i.e., a scale that is used to measured height and weight) situated in a private room.
Potential Risks: None.
Duration: During all visits, before we attach you to our monitoring devices.

Rectal Temperature
Description: In order to estimate internal body temperature, you will self-insert a small (~3mm/0.118 inches in diameter), lubricated, single-use rectal temperature probe about 4 inches. You will insert and remove the probe in a private room.
Potential Risks: Insertion of the temperature probe should not be uncomfortable or painful. There is a very slight risk that you will perforate your rectum. To minimize this risk the temperature probe will be lubricated. Furthermore, rectal temperature will not be measured if you have (or have had) any chronic disorders of the rectum (e.g., cancer, surgery etc.) or if you currently have any related acute conditions (e.g., diarrhea, constipation, etc.).
Duration: During all visits except Visit 1, continually measured.

Blood Sample
Description: A small amount of blood (~3 teaspoons or 15 mL) will be taken from an arm in your vein using aseptic techniques that are guided by the World Health Organization. A sample of your blood will be shipped to our collaborator at Rutgers University for analysis.
Potential Risks: There is a small risk of infection at the site. This will be minimized by using trained personnel who will use aseptic techniques and gloves to properly clean and cover the blood draw site with a bandage.
Duration: Two samples during each visit except Visit 1. A total of ~24 teaspoons (or 120 mL) will taken over the entire study (~6 teaspoons or 30 mL per study visit).

Fecal Sample

Description: You will be given a fecal sample collection kit (DNA Genotek) to take home with you. You will be asked to take a small sample (less than 1 teaspoon or 0.5 mL) of your feces (stool) from your first bowel movement after each study visit following the provided directions. A sample of your feces will be shipped (either by you or a lab member) to our collaborator at Rutgers University for analysis.

Potential Risks: None.

Duration: One sample after study visits 2-5 (4 total samples, less than 4 teaspoons total).

WHAT ARE THE RISKS OF TAKING PART IN THE STUDY?

While participating in the study, the risks, side effects, and/or discomforts include:

Procedures:

Because of your participation in this study, you are at risk for the aforementioned side effects (see Potential Risks above).

Loss of Confidentiality

Any time information is collected there is a potential risk for loss of confidentiality. Every effort will be made to keep your information confidential. However, this cannot be guaranteed.

Other Risks

There also may be other side effects that we cannot predict.

WHAT ARE THE POTENTIAL BENEFITS OF TAKING PART IN THE STUDY?

There will be no direct benefit to you from taking part in this research study. However, we hope that the information learned from this study will provide new information regarding the control of hemodynamics and ventilation during water immersion.

WILL I RECEIVE MY RESULTS?

We may learn things about you from the study activities, but these results are considered research and will not be returned to you.

HOW WILL MY INFORMATION BE PROTECTED?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. No information which could identify you will be shared in publications about this study.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the study investigator and his/her research associates, the Indiana University Institutional Review Board or its designees, and any state or federal agencies who may need to access your medical and/or research records (as allowed by law). State and federal agencies may include the Office for Human Research Protections (OHRP), the US Office of Naval Research Human Research Protection Office, and the Food and Drug Administration (FDA).

A description of this clinical trial will be available on 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.

WILL MY INFORMATION BE USED FOR RESEARCH IN THE FUTURE?

Information or specimens collected from you for this study may be used for future research studies or shared with other researchers for future research. If this happens, information which could identify you will be removed before any information or specimens are shared. Since identifying information will be removed, we will not ask for your additional consent. Your samples will not be used for genetic testing. We will not use the specimens collected as a part of this study for whole genome sequencing, which involves mapping all of your DNA.

WILL I BE PAID FOR PARTICIPATION?

If you agree to take part in this research study, we will compensate you $495 for completing visits 1-5 and $100 for submitting all 4 fecal samples. Money will be paid when you complete or choose to quit the study and will be paid by gift card. If you do not complete the study, you will be compensated only for your time in the study ($15/hour) and $25 for each fecal sample.

If you receive $600 or more in one calendar year from Indiana University, you will be required to provide your Social Security number or tax identification number to Indiana University. You will receive a 1099 tax form the following January and will need to report this payment as income on your federal and state tax returns. You are responsible for paying any state, federal, or Social Security taxes. If you have questions regarding how this impacts your tax return, please contact a tax professional to assist you. If you do not have a social security number or tax identification number, the Internal Revenue Service (IRS) requires Indiana University to deduct 30% from your compensation to pay required taxes on your behalf.

WILL IT COST ME ANYTHING TO PARTICIPATE?

There is no cost to you for taking part in this study.

WHO WILL PAY FOR MY TREATMENT IF I AM INJURED?

In the event of physical injury resulting from your participation in this study, necessary medical treatment will be provided to you and billed as part of your medical expenses. Costs not covered by your health care insurer will be your responsibility. Also, it is your responsibility to determine the extent of your health care coverage. There is no program in place for other monetary compensation for such injuries. However, you are not giving up any legal rights or benefits to which you are otherwise entitled.

If you are participating in research that is not conducted at a medical facility, you will be responsible for seeking medical care and for the expenses associated with any care received.

WHO SHOULD I CALL WITH QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the researcher, Dr. Blair Johnson at 812-855-8699. After business hours or in the event of an emergency, please call Dr. Blair Johnson at the same phone number.

For questions about your rights as a research participant, to discuss problems, complaints, or concerns about a research study, or to obtain information or to offer input, please contact the IU Human Subjects Office at 800-696-2949 or at irb@iu.edu.

CAN I WITHDRAW FROM THE STUDY?

If you decide to participate in this study, you can change your mind and decide to leave the study at any time in the future. The study team will help you withdraw from the study safely. If you decide to withdraw, please notify Dr. Johnson of your decision. Withdrawing will not result in any penalty or loss of benefits to which you are entitled and will not affect your relationship with the Indiana University – Bloomington School of Public Health, or the Human Performance Laboratories.

Your participation may be terminated by the investigator without regard to your consent in the following circumstances: your inability to follow direction, if you cannot attend your scheduled appointments, or if a change in your health history between any of the visits to the laboratory meet any of the exclusion criteria.

PARTICIPANT'S CONSENT

In consideration of all of the above, I give my consent to participate in this research study. I will be given a copy of this informed consent document to keep for my records. I agree to take part in this study.

Participant's Printed Name:_____

Participant's Signature:_____ **Date**:_____

Printed Name of Person Obtaining Consent:_____

Signature of Person Obtaining Consent:_____ **Date**:_____