Informed Consent To Be A Research Participant (ADULT)

A PHASE II TRIAL OF PULSE BUTYRATE PLUS ERYTHROPOIETIN IN BETA THALASSEMIA INTERMEDIA

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BACKGROUND

You are being asked to participate in a research study for the treatment of beta thalassemia intermedia. The only standard treatment for this disease at this time is blood transfusions. The side effect of blood transfusions is a dangerous buildup of iron in the body which can cause serious problems. Blood transfusions may also transmit infectious diseases (such as hepatitis C).

People who have beta thalassemia intermedia have a low level of adult hemoglobin. Fetal hemoglobin is a normal type of hemoglobin that is produced during fetal and neonatal life, and then is no longer produced in large quantities. It can compensate for the hemoglobin that is missing in thalassemia intermedia. Butyrate is a natural chemical compound that can increase the production of fetal hemoglobin in many humans. Erythropoietin is a natural growth factor that stimulates red blood cell production. This study will utilize both therapeutics to attempt to improve (lessen) the anemia that occurs in thalassemia. From 9 to 15 people will be enrolled in this study.

PURPOSES

1) To determine whether treatment with Arginine Butyrate can increase the hemoglobin level in a significant portion of patients with beta thalassemia intermedia.

2) To determine whether the addition of Erythropoietin to the Butyrate will further improve the anemia in thalassemia intermedia patients in addition to that produced by Butyrate alone.

PROCEDURES

If you choose to participate in this study, blood transfusions will be stopped except for acute problems. You will be asked to have a physical examination, as well as blood and urine tests. These baseline examinations will be used to see if there is any abnormality in the liver or kidneys, as well as to see how much fetal hemoglobin you normally produce. If the baseline studies show that you are a good candidate to receive Arginine Butyrate, and you decide to

participate, you will be referred to a surgeon for placement of an indwelling catheter or port device, a tiny tube that stays in a vein with a reservoir, placed. An intravenous port device placement takes approximately one hour, it is done in the outpatient department and it is placed by a surgeon. Problems associated with this catheter or port device include pain, bleeding, infection, or clogging which could lead to the catheter having to be removed. A separate consent form will need to be signed for this procedure. If you already have an indwelling catheter or port device placed for other treatments, you will not need to undergo this procedure.

The first phase of this study is called the Induction Phase. The Induction Phase will determine the optimal dose of Arginine Butyrate that you individually will need to receive to stimulate fetal hemoglobin production. During the Induction Phase, you will be given Arginine Butyrate infusions daily for 5 days a week for 4 weeks. The duration of the infusions may be adjusted slightly to avoid side effects. The duration of the infusion will vary depending on the dose that is tested in you. The 500 mg/kg dose is usually infused over 6 hours. The usual dose required for thalassemia, 800 mg/kg, is infused over 10 hours, usually at night. A high dose, 1200 mg/kg is infused over 14 hours; this dose will be tested only if you do not respond to a lower dose. Blood tests will be done (1-2 times per week) to check your responses. This will be followed by 2 weeks during which you will not receive any drug and additional blood tests will be done to see how you responded to the drug. If there is no increase or only a slight increase in your hemoglobin level after the first course of Arginine Butyrate, you will receive a second course followed by another 2 weeks without any medication. If there is an increase in your total hemoglobin level, you will start the Maintenance Phase of the study. If there is no increase in the total hemoglobin after two induction regimens, you will not continue on the study, and other treatment options will be discussed with you.

During the Maintenance Phase, you will receive the drug Arginine Butyrate as 4-day treatments every other week or a total of 8 nights per month. The Maintenance Phase will last 3 months. Although the Initial Induction Phase will start in the Hematology Clinic or General Clinical Research Center, once you complete teaching on how to care for your device (port) and how to administer the medication, you may receive the medication in your own home with help from visiting nurses or a home care company as needed.

At the end of the Maintenance Treatment Phase, if you do not have any medical contraindications to receiving Erythropoietin, you will be offered participation in the Third Phase of this study which combines Arginine Butyrate and Erythropoietin. You will continue to receive Arginine Butyrate on alternate weeks and Erythropoietin will be added to your treatment. Erythropoietin will be given three times per week by a needle placed under the skin or in your port. We will arrange to have this administered at your home. The Third Phase of this study will last 3 additional months. You will also continue to receive blood tests (once per week).

After completion of this Combination Phase, you may continue receiving the Erythropoietin alone for 12 weeks to see if there is any change in your blood. If your anemia is severe, the Erythropoietin may be given first, alone, before the Butyrate Induction Phase of the study.

If you either decline to receive the Erythropoietin at the end of the Maintenance Treatment Phase or do not qualify to receive the medicine, you will stop receiving Arginine Butyrate. You will

have follow-up blood tests monthly for 2 months or until your hemoglobin level declines to your baseline level to determine how long the effects of Arginine Butyrate persist. At the end of the 3 months on Erythropoietin and Butyrate, the study will be stopped. You will have follow-up blood tests for 2 months to determine how long the effects of Arginine Butyrate and Erythropoietin last. If this treatment was successful in you, future treatment options will be discussed with you at this time. If you are female of child-bearing age, you will be asked to have a urine or blood pregnancy test performed, and you will be asked to use contraception for the duration of the drug treatment.

If you do not tolerate being without blood transfusions, or the study medications are not producing good results, or you are not able to manage receiving the medications on schedule, your participation may be terminated by the study investigator.

SIDE EFFECTS FROM THE DRUGS USED IN THIS STUDY ARE AS FOLLOWS:

Arginine Butyrate is an experimental drug. Arginine Butyrate has been given to many adults and children with blood diseases and other conditions without serious side effects occurring at the doses planned in this study.

The most common reported side effects of Arginine Butyrate are nausea, vomiting, and headaches. These are usually prevented by giving anti-nausea medication before Arginine Butyrate is infused or by giving the medicine more slowly. Some patients who received high doses of Arginine Butyrate (more than twice the dose you will receive) experienced low potassium levels in their blood, which can cause symptoms such as muscle weakness and leg cramps. The potassium level returns to normal when potassium supplements were given and after the treatment was stopped. To prevent this from occurring, food containing potassium will be encouraged. Other uncommon side effects include fatigue, diarrhea, and protein in the urine, which usually does not cause symptoms. Single episodes of low blood pressure, shortness of breath, muscle aches, chest and arm pain, inability to sleep and anxiety were experienced by 5 patients who received much higher doses than you will receive. This drug also has an odor which is unpleasant. Care should be taken not to spill the drug.

The effects of this treatment on a fetus are unknown, therefore, if you are pregnant or nursing a child, you cannot take part in this study. If you are sexually active, you must practice effective birth control measures (oral contraceptives, diaphragm with spermicidal gel, IUD, or condoms) while participating in this study.

Erythropoietin has been used for many years to increase hemoglobin levels. It is a synthetic form of a naturally occurring hormone in the body which normally stimulates red blood cell production and helps red blood cells to live longer. Side effects may include minor bleeding and bruising and discomfort at the site of the injection. High blood pressure, blood clots, and convulsions have occurred in some patients with underlying kidney or heart disease; (kidney failure and serious heart disease are therefore contraindications to receiving Erythropoietin on this study). Other reported side effects include fever, fatigue, headache, cough, diarrhea, nausea, shortness of breath and bone pain. There is a rare possibility that an allergic reaction might occur

(itching, hives, swelling, chills, difficulty breathing). You will be monitored closely for side effects, and your dose will be adjusted if these should occur.

If there are any serious side effects during the study, the treatment with Arginine Butyrate and Erythropoietin will be stopped. The treatment may stop indefinitely or until the problem has resolved. Your doctor has the right to discontinue this treatment at any time without your consent if he/she feels it is in your best interest. You may also be asked to cooperate in having whatever laboratory tests and examinations that are deemed medically necessary. Your routine medical needs will continue to be provided for.

BENEFITS
There are no guaranteed benefits to your participation in this study.

RISKS/BENEFITS
There is no guaranteed benefit to your participation in this study. The risks are as outlined above.

COSTS
Subjects may receive vouchers or payment for up to $25.00/week to cover the costs of local transportation to and from the hospital. No costs for the experimental drug will accrue to your family. No other additional expenses related to the study medications and lab tests are anticipated for you.

ALTERNATIVES
If you decide not to participate in this study, you will continue to receive standard treatment for your beta thalassemia intermedia. Other experimental medicines that increase fetal hemoglobin in some patients are available, such as the cancer medicine Hydroxyurea. These medicines lower other blood counts and may have more serious long-term side effects. Your decision to participate can be changed at any time without affecting your treatment.

PARTICIPATION IN RESEARCH IS VOLUNTARY
You are not obligated to participate in this research. If you choose not to participate, your present and/or future medical care will not be affected in any way, and you will incur no penalty or loss of benefits to which you may otherwise be entitled. Also, if you participate, you may withdraw your consent and discontinue participation at any time without affecting your medical care or benefits to which you may otherwise be entitled. If you decide to discontinue participation, please notify Dr. Perrine at (617) 638-5639, so that arrangements can be made for you to return to your usual treatment program. If any significant new findings are developed during the course of the research which may affect your willingness to continue involvement, we will notify you as quickly as possible.

CONFIDENTIALITY
Your medical records and the records of this study will be handled as confidentially as other medical records, except that representatives of the Institutional Review Board and the FDA may need to see them. Any published data from the study will not identify participants by name.

TREATMENT AND COMPENSATION FOR INJURY

You understand that in the event an injury occurs resulting from the research procedures, medical treatment will be available at Boston Medical Center. However, no special arrangements will be made for compensation, or payment of treatment solely because of your participation in this experiment. You understand that this paragraph is a statement of policy of Boston University, and Boston Medical Center, and does not waive any of your legal rights.

QUESTIONS

If you have any questions regarding the research or your participation in it, either now or at any time in the future, please feel free to ask them. The Research Team, particularly Dr. Susan Perrine, who may be reached at (617) 638-4173, will be happy to answer any questions you have. You may obtain further information about your rights as a research subject by calling the Office of the Institutional Review Board at Boston Medical Center at (617) 638-7207. If any problems arise as a result of your participation in this study, including research related injuries, please call the principal investigator of this study, Dr. Susan Perrine.

SUBJECT'S STATEMENT OF CONSENT

I have read the above descriptions of this research study, and I understand it. I have been informed of the risks and benefits involved, and all of my questions have been answered to my satisfaction. Furthermore, I have been assured that any future questions I may have will be answered by a member of the Research Team. I understand that I will receive a signed copy of this form. I understand that I am free to withdraw this consent and discontinue participation in this research study at any time without prejudice. I voluntarily consent to participation in the described research study.

_____ _____

Patient's signature Date Print patient's name

_____ _____

Physician's signature Date Print physician's name

Valid for use through _____Per IRB_____

STATEMENT OF INVESTIGATOR

I have witnessed that I have fully and appropriately informed the subject of the nature of the above study and have offered to answer any questions he/she may have.

_____ _____

Date Position (physician, principal investigator, nurse)

Initials:_____

LIST OF RIGHTS OF A PARTICIPANT IN A MEDICAL EXPERIMENT
If you are a person participating in a medical study, you must be told:

* The purpose of the study,

* The procedures which will be followed in the study, and the drugs or devices which will be used,

* If there are any other possible treatment, procedures, drugs or devices which can be given (instead of those offered in the study), and the risks or benefits of those other possibilities,

* If there are any discomforts or risks you may expect from participating in the study,

* If any medical treatment will be available to you if complications happen during or after the study,

* If you might benefit by taking part in the study,

* That you may ask any questions about the study and that you must receive answers,

* That you may leave the study at any time, without affecting the quality of care you would receive outside the study,

* That you may freely decide if you want to take part in the study and not be pressured into your decision,

* That you will be given a copy of the written, signed, and dated "Consent to be a Research Participant" form.

Dated: _____

PATIENT, OR PARENT OR GUARDIAN OF:

_____ (NAME OF MINOR CHILD)

Initials:_____