Adult Consent Form

Title of Research Study: Interval Bolus Delivery of Subcutaneous Hydrocortisone via Infusion Pump in Children With Congenital Adrenal Hyperplasia

Investigator: Kyriakie Sarafoglou, MD

For questions about research appointments, the research study, research results, or other concerns, call the study team at:

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Key Information About This Research Study

The following is a short summary to help you decide whether or not to be a part of this research study. More detailed information is listed later on in this form.

What is research?

Doctors and researchers are committed to your care and safety. There are important differences between research and treatment plans:

- The goal of research is to learn new things in order to help groups of people in the future. Researchers learn things by following the same plan with a number of participants, so they do not usually make changes to the plan for individual research participants. You, as an individual, may or may not be helped by volunteering for a research study.
- The goal of treatment is to help you get better or to improve your quality of life. Doctors can make changes to your treatment plan as needed.

Why am I being asked to take part in this research study?

You are a possible participant in the study because you have been diagnosed with congenital adrenal hyperplasia (CAH). Children between the ages of 3-18 years old may be eligible to participate in this study.

What should I know about being in a research study?

- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

Why is this research being done?

The purpose of this study is to find out if giving hydrocortisone (HC) under your skin with the study device more closely mimics the rhythms of cortisol production in your body, and to find out if this improves control of hormones in your body. We will compare children taking oral HC to children receiving HC through the study device.

Current therapies include chronic hydrocortisone treatment. This is not ideal because it results in alternating too-low and too-high levels of cortisol in the blood. Low cortisol has side effects like early puberty, polycystic ovarian syndrome (PCOS) and infertility. High cortisol has side effects like osteoporosis, short height, and a higher risk of cardiovascular disease as an adult. In this study, we hope to learn if the hydrocortisone given under the skin is a good alternative to the current chronic hydrocortisone therapies

How long will the research last?

The length of study treatment period for which you will participate is 20 weeks. It will include three inpatient admissions and four outpatient visits to the Prism Clinical Research Center (1000 Westgate Dr #149, St Paul, MN 55114). There will also be home visits made by the nurse coordinator during the 6 week trial while on the SQHC pump.

What will I need to do to participate?

In this study, you will be asked to return for all study visits described below, to take your medicine as directed, and to follow instructions from study staff.

More detailed information about the study procedures can be found under ***"What happens if I say yes, I want to be in this research?"***

Is there any way that being in this study could be bad for me?

Hydrocortisone injections may cause irritation or redness at the injection site. More detailed information about the risks of this study can be found under ***"What are the risks of this study? Is there any way being in this study could be bad for me? (Detailed Risks)"***

Will being in this study help me in any way?

There are no benefits to you from your taking part in this research. We cannot promise any benefits to others from your taking part in this research.

What happens if I do not want to be in this research?

You may decline to participate and it will not be held against you.

Your participation in this study is your choice. You may choose either to take part or not to take part in the study. If you choose not to participate, you could continue on your standard treatment, which is to take hydrocortisone 3-4 times a day by mouth.

Detailed Information About This Research Study

The following is more detailed information about this study in addition to the information listed above.

How many people will be studied?

We expect about 8 people will be in this research study.

What happens if I say "Yes, I want to be in this research"?

If you would like to be in this study, the following study procedures would be done at the following visits:

Weeks 1-8 (Oral HC)

Week 1 (Admission 1)

During the first week of the study and while you are on oral hydrocortisone therapy, you will be admitted into the research unit for approximately 36 hours.

- You will have a physical exam assessing height, weight, blood pressure and heart rate.
- You will be asked for fill out quality of life questionnaires and a survey on your quality of sleep and a survey on your mood.
- You will also take a computer based test examining cognitive domain measures. 'Cognitive domain' means how you think, know, remember, judge, and problem solve.
- During Admission 1, you will take your usual doses that will be administered at 3 standardized dosing times (6 a.m, noon, 6 pm) for the 24-hr serial blood sampling study: Changes from usual dosing times are expected to be small and inconsequential.
- Immediately prior to the morning dose at 6am, a blood sample will be obtained for measurement of cortisol, 17-hydroxyprogesterone (17OHP), androstenedione (D4A) and adrenocorticotropic hormone (ACTH). 17OHP and D4A are hormones that are usually increased in children who cannot make cortisol, and levels of these two hormones usually drop when hydrocortisone therapy is started. Samples will then be obtained at 0.5, 1, 1.5, 2, 3, 4, and 6 hrs after the first dose. The same sampling intervals will be used following the noon and 6 pm doses, with additional samples collected during the night at 2 am, 4 am, and 6 am. The total blood drawn over 36 hrs will be approximately 75 ml (about 5 tablespoons). An IV will be placed to avoid multiple needle sticks.
- Your urine will be collected over a 24 hour period. Approximately four tablespoons will be saved for future analysis.
- You will give saliva samples, collected during the day at 6am, 7am, 12pm, 1 pm, 6 pm and 7pm (6 samples total). You will be asked whether you want to have the saliva samples from this study to be kept by the lab for possible future research.
- You will be given a diary to take home and use during the study. This will cover items such as any signs or symptoms, adverse events and any changes in medications you may have during the study. We will ask you to fill this out and bring back at each visit.

Weeks 1-6

Upon discharge, you will continue taking your regular oral hydrocortisone does at your usual times for 6 weeks.

Weeks 6

- The research nurse will visit you at home for an assessment of how you are doing.
- An Actigraph Link accelerometer watch will be given to you to monitor daily activity and sleep patterns for one week. These will be monitored by study personnel.

Week 7 (Admission 2: SQHC Pump 33 hours)

You will be re-admitted for training using the Crono P subcutaneous HC infusion pump and include 24 hour serial blood sampling while on the SQHC pump.

- You will have a physical exam assessing height, weight, blood pressure and heart rate.
- Training will emphasize proper aseptic catheter placement, care of the insertion site, reconstituting the solution and filling the infusion syringe. HC sodium succinate (SOLU-

CORTEF) sterile powder will be used for the SQHC pump as it is FDA approved for intramuscular and intravenous routes for CAH. You will be instructed how to mix and dilute the solution with sterile normal saline. You will already be familiar with HC sodium succinate solution as this is what you use for emergencies when you are not able to take oral medication.

- Pump therapy during this admission will begin at 9 pm and continue for 33 hours. Doses from the pump will be delivered at 9:00 pm, 12:00 am, and 3:00 am. After the 6 am dose from the pump is delivered, 24-hr serial blood sampling will begin using the same sampling schedule of cortisol, 17OHP, ACTH and D4A as the first admission. An IV will be placed to avoid multiple needle sticks.
- Urine sampling will be collected using the same schedule as the first admission.
- Saliva sampling will be collected using the same schedule as the first admission at 6am, 7am, 12pm, 1 pm, 6 pm and 7pm (6 samples total).
- You will be given and instructed on how to use an automatic, upper arm blood pressure monitor with a cuff appropriate for your size. One week prior to the SQHC pump treatment, while you are still on oral HC, we will ask you to measure and log your blood pressure daily in the morning, after 5 minutes rest. When you are on the pump, we will ask you to measure and log your blood pressure daily in the morning.

Weeks 7-8

After completing the serial blood sampling study, you will be discharged from the research facility and continue on your usual HC oral dosing schedule for 2 weeks prior to initiation of the SQHC pump. During this time, cortisol, 17OHP, ACTH and D4A concentrations will be analyzed to determine that the pump has delivered HC as expected and cortisol, 17OHP, ACTH and D4A concentrations are in an acceptable range.

Week 8

The research nurse will call you to talk about how you have been doing since your last visit. They will go over your study diary and ask about medicines you may have taken.

<u>Weeks 9-14 (SQHC Pump)</u>

Week 9

You will have a visit with Dr. Sarafoglou and the study nurse coordinator at Prism for initiating the 6-wk SQHC pump phase of the study.

Weeks 9-12

- During the first 2 weeks of using the pump, four supervised home visits by the nurse coordinator coinciding with the time of changing the infusion sites every 72 hours will be scheduled.
- You will change your infusion site every 72 hours for the duration of the pump are of the study.
- The nurse coordinator will visit you at home weekly for safety monitoring, which includes checking the pump site, and measurement of cortisol, 17OHP, ACTH and D4A concentrations during the SQHC pump period. During the home visits, along with the blood draws and saliva will be collected. One saliva sample will be measured through the VerOFy® cortisol (VCORT) device at that time. This device may not be available at all visits but the nurse coordinator will

tell you if we are completing that sample or not. The remaining salivary sample will be sent to Quest Diagnostics lab for cortisol measurements

Week 13

- The research nurse will visit you at home for an assessment of how you are doing. They will check your pump site.
- An Actigraph Link accelerometer watch will be given to you to monitor daily activity and sleep patterns for one week.
- During the home visits, along with the blood draws and saliva will be collected. One saliva sample will be measured through the VerOFy® cortisol (VCORT) device at that time. This device may not be available at all visits but the nurse coordinator will tell you if we are completing that sample or not. The remaining salivary sample will be sent to Quest Diagnostics lab for cortisol measurements.

Week 14 + 5 days (Admission 3)

- You will be admitted for a final SQHC pump 24-hr serial blood sampling. This study will occur at the 6:00 am pulse using the same sampling schedule of cortisol, 17OHP, ACTH and D4A as the previous two admissions. Urine and saliva samples will collected using the same sampling schedule as admission 1 and 2. Once the 24-hr sampling study is complete, you will discontinue use of the pump and resume your usual oral HC regimen. An IV will be placed to avoid multiple needle sticks.
- You will have a physical exam assessing height, weight, blood pressure and heart rate.
- Quality of life, sleep and mood surveys, along with the cognitive domain measures will be repeated.

<u>Weeks 15-20 (Oral HC follow-up)</u>

Weeks 15 (+1 day) - 20

We will continue to follow you with weekly phone calls

Week 19

- The nurse coordinator will visit you at home for an assessment of how you are doing.
- An Actigraph Link accelerometer watch will be given to you to monitor daily activity and sleep patterns for one week.

Week 20

- You will have a visit with Dr. Sarafoglou and the study nurse coordinator. You will have a physical exam assessing height, weight, blood pressure and heart rate. Quality of life, sleep and mood surveys, along with the cognitive domain measures will be repeated.

What else do I need to know?

Due to the COVID-19 pandemic, to be admitted to the Prism Clinical Research Center you have to come to the Prism site at least 3 days before the study visit to complete a COVID-19 test. A negative COVID-19 test is required before admitting to the center. Only one accompanying family member is allowed to be tested and to be onsite with the child at a time. Our study staff will let you know if there are any positive tests and the PI will recommend next steps based on public health guidelines. If this testing requirement changes during participation in the study, the study staff will let you know.

Some home visits may be able to be done remotely with the study coordinator, and PI if necessary. The study coordinator will let you know what visits these may be done at and what the study team would need from you at the visit. This may include having taken your blood pressure with the cuff provided and having your study diary available. These visits can be done over a secured method such as a phone line or video method option called Zoom. The study coordinator will help set this up for you.

What happens if I say "Yes", but I change my mind later?

At any time, you may decide to withdraw from the study. If you withdraw, no more information will be collected from you. When you indicate that you wish to withdraw, the information already collected from you will be used in the study because they will not be able to remove it from the information they have gathered.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study requirements; or if the study is stopped.

Choosing not to be in this study or to stop being in this study will not result in any penalty to you or loss of benefit to which you are entitled. Meaning, your choice not to be in this study will not negatively affect your right to any present or future medical treatment.

What are the risks? Is there any way being in this study could be bad for me?

While on study, you may experience all, some, or none of the risks described below. We will work with you to lessen the risks whenever possible.

Risks of hydrocortisone (HC) sodium succinate: HC sodium succinate (100 mg/ml) will be used as it is FDA approved for intramuscular (IM) and IV routes for CAH. The HC solution may cause minimal injection site irritation and reactions.

Venipuncture: Drawing blood may cause pain, bruising, lightheadedness, or, on rare occasions, infections.

Risk of loss of privacy: There is a risk that your study medical records will be viewed by those outside the study. Precautions taken to avoid breach of privacy include using study ID numbers rather than names on labs/documents that are not a component of the clinical record, maintaining electronic records on password protected and secure computers serviced by the University of Minnesota Academic Health Center, and storing study binders in a locked storage area within the PI and study coordinator.

Crono P pulsatile subcutaneous infusion pump: The pump settings will always be set by Dr. Sarafoglou or the study nurse coordinator. They will be on call 24/7 to answer any concerns and questions related to the pump. Training of you on the use of the pump, including the infusion sets which will be used, and the operational functions of the alarms will begin during the first admission (Week 1).

Similar to continuous SQ insulin infusion, which is the standard treatment for children with diabetes, SQHC uses similar infusion sets that have to be changed every 3 days in order to prevent infection or occlusion Occlusions are possible with SQ infusion pumps. With insulin, occlusion episodes are rare

when the cannula is changed within 72 hours as we will do. In addition, HC sodium succinate is more water soluble than insulin and not as likely to crystallize. During febrile illness, you will be instructed to start standard oral HC doses as per our standard oral stress dosing protocol. If unable to take oral HC, the intramuscular stress HC succinate dose protocol will be followed.

Pump malfunction: In the case of a pump malfunction, you will switch to oral hydrocortisone therapy until the pump is replaced. If an occlusion occurs, the cause can be rectified by unkinking the tubing, replacing tubing, or relocating the subcutaneous insertion site. A clinician will always be on call to address issues that arise. The risk of a pump malfunction or occlusion that results in several missed doses is not a life-threatening situation.

A pump malfunction may cause early symptoms of low cortisol, such as headache, dizziness, and fatigue. If the pump malfunctions, it would trigger an alarm. As a backup, you will be given and trained on a blood pressure monitor and log your blood pressure while on study. You will also be shown how to inspect the injection site, tubing, and syringe volume of the pump. If you can't find any problems with the pump and your blood pressure appears outside of the normal range for three measurements, you would come to the clinic for an exam and the study team would help look at the pump.

Will it cost me anything to participate in this research study?

Taking part in this research study will not lead to any costs to you.

What happens to the information collected for the research?

Efforts will be made to limit the use and disclosure of your personal information, including research study records, to people who have a need to review this information. We cannot promise complete secrecy. Organizations that may inspect and copy your information include the IRB and other representatives of this institution.

Will anyone besides the study team be at the consent meeting?

You may be asked by the study team for your permission for an auditor to observe the consent meeting (or a recording of the consent meeting). Observing the consent meeting is one way that the University of Minnesota makes sure that the rights of research participants are protected. The auditor is there to observe the consent meeting, which will be carried out by the people on the study team. The auditor will not record any personal (e.g. name, date of birth) or confidential information about you. The auditor will not observe the consent meeting (or a recording of the consent meeting) without your permission ahead of time.

Whom do I contact if I have questions, concerns or feedback about my experience?

This research has been reviewed and approved by an IRB within the Human Research Protections Program (HRPP). To share feedback privately with the HRPP about your research experience, call the Research Participants' Advocate Line at 612-625-1650 (Toll Free: 1-888-224-8636) or go to z.umn.edu/participants. You are encouraged to contact the HRPP if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

Will I have a chance to provide feedback after the study is over?

After the study, you might be asked to complete a survey about your experience as a research participant. You do not have to complete the survey if you do not want to. If you do choose to complete the survey, your responses will be anonymous.

If you are not asked to complete a survey after the study is over, but you would like to share feedback, please contact the study team or the Human Research Protection Program (HRPP). See the "Who Can I Talk To?" section of this form for study team and HRPP contact information.

What happens if I am injured while participating in this research?

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to you or your insurance company. If you think that you have suffered a research related injury, let the study physicians know right away.

Will I be compensated for my participation?

You will be paid $500 for each admission visit, $50 for each outpatient visit and an additional $50 at the completion of the week 20 visit, in the form of a gift card. If you complete all study visits, this is a total of $1700 for the entire study.

Payment you receive as compensation for participation in research is considered taxable income. If payment to an individual equals or exceeds $600 in any one calendar year, the University of Minnesota is required to report this information to the Internal Revenue Service (IRS). Research payments to study participants that equal or exceed $600 during any calendar year will result in a FORM 1099 (Miscellaneous Income) being issued to you and a copy sent to the IRS.

Use of Identifiable Health Information

We are committed to respect your privacy and to keep your personal information confidential. When choosing to take part in this study, you are giving us the permission to use your personal health information that includes health information in your medical records and information that can identify you. For example, personal health information may include your name, address, phone number or social security number. Those persons who get your health information may not be required by Federal privacy laws (such as the 1099 Rule) to protect it. Some of those persons may be able to share your information with others without your separate permission. Please read the HIPAA Authorization form that we have provided and discussed.

The results of this study may also be used for teaching, publications, or for presentation at scientific meetings.

Optional Elements

Yes, I agree	No, I disagree	
		Quest Diagnostics Lab may retain any leftover saliva samples taken during the study. These samples may be used for other research not related to this study. These samples will be retained in non-identifiable form, meaning that there will be no information associated with the samples that will allow anyone to readily ascertain my identity.

Adult Consent Form

Signature Page

Your signature documents your consent to take part in this research.

_____

Printed name of participant

_____ _____

Signature of participant Date

_____

Printed name of person obtaining consent

_____ _____

Signature of person obtaining consent Date