Study Title: Safety and Pharmacokinetics of Positively Charged Compounds by Transdermal Administration by a Novel Wireless Iontophoresis Device

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INTRODUCTION

You are being asked to participate in a research study that is supported by the James J. Peters Veterans Affairs Medical Center (JJPVAMC). This research study is being performed at JJPVAMC. Before you decide to take part, it is important for you to know why the research is being done and what it will involve. This includes any potential risks to you, as well as any potential benefits you might receive.

You will read the information below closely, and you will discuss it with your family and friends if you wish. You can also ask one of the study staff members if there is anything that is not clear to you or if you would like more details. You will take your time to decide. If you do decide to take part in this study, your signature on this consent form will show that you received all of the information below, and that you were able to discuss any questions and concerns you had with a member of the study team

1. Purpose of study and how long it will last:

You are being asked to participate in a research study because you are an able-bodied individual between the ages of 18 and 70. The purpose of this study is to determine the safety of positively charged compounds (medications - e.g., vitamin B12, neostigmine, and glycopyrrolate) administered transcutaneously (through the skin) by a wireless iontophoresis (ION) device. The study is also looking at the delivery of these substances into the circulation over time.

If you consent to participate, you will visit our laboratory 3 times for approximately 2-3 hours each time. A copy of this form will be given to you and a copy will be kept by the JJPVAMC research team. There may be words in this consent form that you do not understand. If you do not understand a word or sentence, please ask the person who is reviewing this document with you to explain. The study is funded by Congressionally Medically Directed Funds – Department of Defense (Grant #SC180166). All study procedures will take place in the SCI Research Laboratory of the Bronx VA Medical Center.

Participants:
You will be one of six (6) participants in this study. You are being asked to participate because the following criteria apply to you.

Inclusion Criteria:
You are eligible for participation if all of the following apply you.

1. Male or female;
2. Able-bodied;
3. Between the ages of 18-89 years old.

Exclusion Criteria:
If any of the below statements apply to you, you need only tell the researcher that one or more of the statements pertain to you. To ensure your privacy and confidentiality, you need not reveal which of the statements apply to you. If you choose to tell the investigator which of the statements apply to you, the information will be kept strictly confidential. You will inform the researcher if any of the following statements apply to you.

1. Previous adverse reaction or hypersensitivity to electrical stimulation;
2. Known sensitivity (prior reaction or allergy) to neostigmine or glycopyrrolate;
3. History of mechanical obstruction (physical blockage) of the GI or urinary tract (e.g., due to scar tissues forming after surgery, gallstones);
4. Myocardial infarction (heart attack) within 6 months of trial;
5. Malignant and/or uncontrollable hypertension (high blood pressure) defined by a blood pressure reading of 140/100 mmHg or higher with or without taking 3 or more different classes of anti-hypertensive medications (drugs used to treat high blood pressure);
6. Organ damage or past failure (heart & kidney) and/or transient ischemic attack/cerebrovascular accident (TIA-CVA, or stroke) as a result of hypertension. Organ damage may be defined as impairment to any major body part/organ that results in its ability to function and causes illness. Heart failure is a condition that may be identified by the physical findings of peripheral edema (swelling), enlarged liver, fluid around the lungs (pleural effusion), and/or difficulty breathing; the signs of heart failure may be usually identified by documenting a reduced cardiac output. Kidney failure is diagnosed by a

severe reduction in glomerular filtration rate, usually <30 ml/min. End stage renal failure results in fluid accumulation/edema, cardiac friction rubs, and symptoms of azotemia (generally feeling sick);

7. Known past history of coronary artery disease or bradyarrhythmia (slow irregular heartbeat, less than 60 beats per minute);
8. Symptomatic orthostatic hypotension (low blood pressure with possible dizziness/fainting);
9. Deep brain stimulation;
10. Pregnancy (men and women who are sexually active and of childbearing potential must utilize a method of contraception and agree to maintain a contraceptive method until completion of study);
11. Lactating, nursing females;
12. Inability to provide informed consent signaled by a Montreal Cognitive Assessment Test (MoCA) score of 20 or less. This test is used to detect mild cognitive impairment;
13. Concurrent illness and fever;
14. Allergy to sodium lauryl sulfate, silver chloride, agarose gel, citric acid, isopropyl alcohol, or polyethylene glycol;
15. Evidence of bradycardia (as defined by a heart rate of less than 60 per minute) or an abnormal electrocardiogram (EKG) at baseline. An EKG measures the heart's electrical signals and can detect heart problems;
16. Currently treated with any cholinesterase inhibitor (e.g., medications for treatment of Alzheimer's disease, Parkinson's disease, Lewy body dementia, myasthenia gravis) or anti-depressants;
17. Concomitant chronic gastrointestinal disease such as inflammatory bowel disease (IBD), irritable bowel syndrome with constipation (IBS-C), or other causes of difficulty with stool evacuation such as hypothyroidism (underactive thyroid);
18. Have any of the following conditions: glaucoma, autonomic neuropathy, ulcerative colitis, prostate hypertrophy, hiatal hernia, hepatic disease (as defined by acute or chronic hepatitis secondary to viral etiology, alcoholism, obesity, autoimmune conditions, or genetic conditions), concern for incomplete or partial intestinal obstruction, ileostomy, colostomy, cardiac arrythmia, myasthenia gravis, peritonitis;

19. Taking any medication that could result in adverse reactions with neostigmine and/or glycopyrrolate, as determined by a study physician;
20. Concurrent participation in a research study.

2. Description of the Study Including Procedures to be Used:

The purpose of this study is to determine the safety of positively charged compounds (medications - e.g., vitamin B12, neostigmine, and glycopyrrolate) administered through the skin by a wireless iontophoresis device. The study is also looking at the delivery of these substances into the circulation over time. If you consent to participation in this research study, the following procedures will be completed:

Overview:

You will have a baseline EKG; if any abnormalities are found, you will not be allowed to participate in this study. If no abnormalities are found, you will receive vitamin B12 (15 mg) through your skin using a wireless iontophoresis ION device. You are also being asked to return for a second visit to receive NEO (0.07 mg/kg) and GLY (0.014 mg/kg) through your skin using a wired ION device (Dynatron iBox). You will be asked to return for the third and final visit, at least 24 hours after the second study visit, to receive NEO (0.07 mg/kg) and GLY (0.014 mg/kg) through your skin by a wireless ION device. This dose has been shown to be safe and effective in previous participants of related studies.

EKG:

Electrodes (small sticky pads) will be placed on you to continuously monitor your heart rate. Heart rate will be monitored and recorded to ensure there are no abnormalities.

IV line insertion:

Following filling out paperwork, we will leave you in the privacy of the room to put on a gown which will protect your clothing. Once you are done, we will insert an intravenous catheter into one of your larger veins in the arm by a study physician. This IV catheter will be used as a blood draw access point. It will also allow the administration of atropine as an anticholinergic antidote or physostigmine as a cholinergic antidote in case of an emergency.

Blood Draws:
We will draw blood 10 times for two hours. Your name is not going to be written on the blood sample tubes or associated with the results any of the networked computer systems. A total of 30 vials of blood, each one approximately one teaspoon, are going to be collected and kept. In order to clear saline from tubing, 8 vials of approximately 0.5 mL blood will be collected and discarded.

Iontophoresis (ION) Preparation:
One iontophoresis device we are using is a Dynatron® iBoxTM. This device is approved by the U.S. Food and Drug Administration for delivery of salts of drugs of which both neostigmine and glycopyrrolate are examples. We will clean a 2x2in area on your upper thigh with alcohol skin prep pads. If necessary, the hair will be clipped. On the first visit, the patch with vitamin B12 (15 mg) will be placed on the prepared skin. On the second and third visits, the patch with NEO (0.07 mg/kg) and GLY (0.014 mg/kg) will be placed on the prepared skin.

Vitamin B12 Administration:
The wireless ION device will deliver vitamin B12 (15 mg) over a period of 20 minutes. You will be monitored for approximately 120 minutes.

NEO and GLY Administration:
The iBOX (second study visit) or wireless ION device (third study visit) will deliver the NEO (0.07mg/kg) and GLY (0.014 mg/kg) at the same time over a period of 20 minutes. You may have to defecate soon after receiving the two medications. You will be monitored for approximately 120 minutes.

Skin Observation:
After administration of the agents by ION, your skin will be inspected for the potential for irritation and/or burns; a digital image will be acquired of the site at which the device was placed.

Blood Pressure (BP) and Continuous Heart Rate (HR) Monitoring:
Your heart rate and blood pressure will be recorded at baseline and sequentially monitored through the experiment using and automated portable blood pressure and heart rate monitor (IVY 101R, IVY Biomedical, Branford, CT). These measurements will be recorded at baseline and intervals after drug administration (5, 10, 20, 30, 40, 60, 90, and 120 minutes). Heart rate will be monitored by a study investigator for 120 minutes for all three study visits.

Pulse Oximetry:
Continuous monitoring of systemic oxygenation will be performed by a hand digit pulse oximeter.

Bowel Sounds:
Your bowel sounds will be assessed at baseline and post drug administration at intervals for an hour. A stethoscope will be pressed lightly on your abdomen to listen for bowel sounds, 30 seconds per abdominal quadrant. Five or fewer bowel sounds will be deemed hypoactive and more than 30 bowel sounds in 1 minute will be deemed hyperactive.

Symptoms Survey:
You will be monitored at intervals described in Table 1 for the following symptoms and signs: salivation (increase/decrease), difficulty in swallowing, syncope, blurry vision, eyelid and other muscle fasciculation or cramps, diaphoresis, headache, and abdominal discomfort.

Blood Collection:
Approximately 4 mL (~1 teaspoon) of venous blood will be collected at each of the following timepoints: baseline, 5, 10, 20, 30, 40, 60, 90, and 120 minutes. This will used to measure changes in concentration of the drugs in your blood over time.

Table 1										
Time Points (in minutes)	**Baseline**	**0**	**5**	**10**	**20**	**30**	**40**	**60**	**90**	**120**
Start of (1) vitamin B12* or (2) NEO + GLY administration		x								
Blood Collection (3-4mL per vial)	x		x	x	x	x	x	x	x	x
Heart Rate (HR)	x	x	x	x	x	x	x	x	x	x
Pulse Oximetry (SPO2)	x	x	x	x	x	x	x	x	x	x
Blood Pressure (BP)	x	x	x	x	x	x	x	x	x	x
Assessment of Bowel Sounds	x	x	x	x	x	x	x	x	x	x
Symptoms	x	x	x	x	x	x	x	x	x	x

The concentrations (in mg/mL) and doses (in mg/kg) can be found below. Formulations of NEO and GLY made specifically for administration via Iontophoresis (through the skin) are not commercially available. The JJPVAMC research pharmacy will therefore compound (prepare) these medications on a per-prescription basis for study visits 2 and 3.

Iontophoresis of Neostigmine and Glycopyrrolate (Visits 2 and 3)
Drug Concentration and Dose
Neostigmine Methylsulfate (powder), PCCA; 0.07 mg/kg ***Not to exceed 10 mg or 0.07 mg/kg***
Glycopyrrolate, USP (powder), PCCA; 0.014 mg/kg ***Not to exceed 2 mg or 0.014 mg/kg***

* These agents will be compounded by the JJPVAMC Research Pharmacy; compounded pursuant to a prescription under FD&C Act Section 503A, following USP <795> for non-sterile compounding.

3. Description of any Procedures that may Result in Discomfort or Inconvenience:

- Because this research may have unknown effects on an unborn child and should not be performed during pregnancy, it is necessary for a pregnancy test to be performed to rule out the possibility that you may be pregnant. To the best of your knowledge, you are not

pregnant at the present time. You also agree to avoid becoming pregnant (use contraceptives, take precautions against becoming pregnant, etc.) during this study.

- There may be some risks associated with this experiment that we are not aware of because this is as of yet an unexplored area of healthcare science.

EKG:
You may experience some discomfort when the electrodes are removed from your skin and some skin irritation at the site of electrode placement.

IV Line Insertion:
Insertion of an IV catheter will elicit pain and upon removal there may be a brief and small amount of bleeding from the insertion site. There is a potential risk of developing a bruise or infection at the site of skin puncture and a small risk that you will faint during the IV insertion.

iBOX and wireless ION:
The small amount of electric current may cause a tingling sensation at the site of the electrode attachment. One iontophoresis device we are using is called a Dynatron iBox which is made by Dextronics. It is approved by the U.S. Food and Drug Administration for delivery of salts of drugs of which both neostigmine and glycopyrrolate are two examples.

Neostigmine + Glycopyrrolate:
You may feel a slight discomfort due to the administration of NEO + GLY. Neostigmine has potential side effects that include increased salivation, decreased heart rate, difficulty breathing, sweating, increased flatulence, and urination. In most cases, the side effects are mild and are resolved within 1 hour. Glycopyrrolate (also known as Robinul) has potential side effects that include dry mouth, increased heart rate, blurred vision, light sensitivity, urinary hesitancy, and nausea.

4. Expected Risks of Study:
In case that we discover a major clinical finding during this experiment, we will notify your treating physician and Dr. Cardozo, the Principal Investigator. There may be some risks

associated with this experiment that we are not yet aware of, since this is as of yet an unexplored area of healthcare science.

EKG:
You may experience some skin irritation when the electrodes are removed.

IV Line Insertion:
The risks include the possibility of pain and bruising at the site of skin puncture and rarely, fainting or infection. Insertion of the IV catheter will elicit pain and upon removal there may be a brief and small amount of bleeding from the insertion site. There is a potential risk of developing a bruise or infection at the site of skin puncture and a small risk that you will faint during the IV insertion.

Blood draw:
There is risk of skin, blood and tissue infections, fainting, pain, nerve or tendon damage, arterial puncture and air embolization. The most common adverse effect is bleeding after catheter removal. If it occurs, it will be addressed before you leave.

iBOX and wireless ION:
The small amount of electric current is very unlikely to be capable of causing significant harm. But the possibility of a minor (first degree over a tiny area) burn exists if the pain occurs for over 2 minutes and the current is not turned off. We will continuously monitor for signs and symptoms of pain and turn off the small amount of electric current as soon as you notify the researchers that there is pain, burning or sensation at or around the patch. There may be additional risks associated with the wireless iontophoresis device that we are not aware of because this is a prototype that has not been tested in human subjects to date.

Neostigmine + Glycopyrrolate:
Neostigmine has been reported to occasionally result in significant slowing of heart rate that may result in a drop in blood pressure and require an injection of medication to reverse these effects. It is known that glycopyrrolate reduces these effects on the heart rate and blood

pressure. Allergic reactions have been reported but are extremely rare. You have been carefully selected to minimize the risk of these complications.

Vitamin B12:
There are no known risks associated with a high administration of vitamin B12.

5. Expected Benefits of the Study:

- You will assist us in understanding the safety of using a newly developed and easy to use wireless ION device, as well as its ability to deliver medications into the circulation.
- There may be no direct benefit to you from this study, but any information we obtain from this study may help others to control their incontinence and constipation. If an abnormality that may be clinically treated is identified during the study, it will be brought to you and/or your physician's attention.

6. Other Treatments Available:
This is not a treatment study and should not take the place of any standard treatments that you receive (unless instructed by your primary care physician during study). If you do not participate in this study, you can still receive standard treatment for your conditions. Abrupt termination from this study should have no impact on your medical condition.

Oral and rectal laxatives such as bisacodyl, magnesium citrate and castor oil are used by people with chronic constipation to increase the peristalsis and speed up the onset of bowel evacuation. Their effect is highly unpredictable in timing and power, unlike the treatment approach that we are currently investigating by administering neostigmine and glycopyrrolate which will cause a predictable bowel emptying within 30 to 60 minutes.

7. Use of Research Results:
The researchers will let you and your physician know of any significant new findings made during this study which may affect your willingness to participate in this study. All research material generated from the study will remain in the possession of Dr. Christopher Cardozo and his study team at the JJPVAMC.

Your research records will be maintained according to the requirements of the JJPVAMC as follows:

Data Collection, Storage, and Transfer:

- Your coded electronic data without your name, or other identifying information, will be stored on secured networks, behind electronic security systems, in access-restricted folders.
- Hard copies of your data will be stored in a locked file cabinet behind 2 locked doors.

Access to the research materials generated from the study will be restricted to Dr. Cardozo's research team. All electronic and hardcopy Records will be retained according to National Archives and Records Administration, in accordance with Records Schedule RCS-10-1. If results of this study are reported in medical journals or at meetings, you will not be identified by name, by recognizable photograph, or by any other means without your specific consent. No information by which you can be identified will be released or published unless required by law. In order to comply with federal regulations, research records identifying me may be reviewed by the following:
The study sponsor [Congressionally Medically Directed Funds- Department of Defense] of this study, authorized representatives of the JJPVAMC (e.g. Institutional Review Board, Research Compliance Officer) and VA, including the Office of Research Oversight (ORO), Federal Agencies such as the Government Accounting Office (GAO), VA Office of Inspector General (OIG), Food and Drug Administration (FDA), and the Office for Human Research Protections (OHRP).

8. Special Circumstances:

- We will write a brief note in your VHA electronic medical record along with the signed HIPAA and the Informed consent form that authorize us to access your medical record for research purposes only.
- Dr. Korsten is a named inventor of two patents filed by the Department of Veterans Affairs related to methods for bowel care in individuals with constipation. The outcome of this research project could affect the value of these patents.

9. Compensation and/or Treatment in the Event of Injury:

The VA must provide necessary medical treatment to a research subject injured by participation in a research project approved by a VA R&D Committee and conducted under the supervision

of one or more VA employees. Further information about compensation and medical treatment may be obtained from the medical administration service at this VA medical center.

10. Voluntary Participation:
You are not required to take part in this study; your participation is entirely voluntary you can refuse to participate in this study or withdraw your participation in this study after you consent without penalty or loss of VA or other benefits to which you are entitled.

11. Termination of Participation:
You can refuse to participate now or you can withdraw from the study at any time after giving your consent. This will not interfere with your regular medical treatment if you are a patient.
The PI retains the right to terminate your study participation for any reasons, including reasons of non-compliance, failure to show up for study visits or for medical reasons.

12. Costs and Reimbursements:
As a veteran or non-veteran, you will not be charged for any treatments or procedures that are part of this study. For veterans who are required to pay co-payments for medical care and services provided by VA, these co-payments will continue to apply for medical care and services provided by VA that are NOT related of this study. You have been told that you will receive $180 for your three days of participation in this study—that is, you will receive $60 for each study visit. If you complete the study partially, you will be reimbursed $60 for each day of participation. You will receive payment 6-8 weeks after the completion of the screening visit. You understand that to receive reimbursement through EFT, you will be required to provide the research staff information that includes the name of your bank, routing number and account number.

13. Contact Person(s):
- To obtain answers to questions about the research, report or seek treatment for a research-related injury, or to voice concerns or complaints about the research contact the following:
    - During the Day: [Christopher Cardozo, MD: (718) 584-9000 x1828], 7th floor in the research building, room 7A-13]
    - After Hours: [Christopher Cardozo, MD: (917) 923-3569]

- To voice concerns or complaints about the research from someone outside of the research team, contact the following: Mary Sano, Ph.D. ACOS/R&D Program by requesting an appointment at (718) 741-4228 hospital extension 4228, first floor in the research building, room 1F-01C.

Conflict of Interest Disclosure:
Dr. Korsten is a named inventor of two patents filed by the Department of Veterans Affairs related to methods for bowel care in individuals with constipation. The outcome of this research project could affect the value of these patents.

RESEARCH SUBJECTS' RIGHTS: I have read or have had read to me all of the above. Dr. Christopher Cardozo or his delegate has explained the study to me and answered all of my questions. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available to me.

I understand that I do not have to take part in this study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this study at any time without penalty or loss of VA or other benefits to which I am entitled.

The results of this study may be published, but my records will not be revealed unless required by law.
This study has been explained to me. I have had a chance to ask questions. I voluntarily consent to participate in this study. I will receive a signed copy of this consent form.

Subject Signature	Date	Time

Person Obtaining Informed Consent (Print Name) (Investigator or Delegate as indicated on Assurance Page)	Signature of Person Obtaining Informed Consent	Date