Study Title: Pharmacokinetics of Neostigmine and Glycopyrrolate after Intravenous and Transcutaneous Administration by Iontophoresis

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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 in which we are looking at the pharmacokinetic behavior of Neostigmine and Glycopyrrolate. Pharmacokinetics is a study of the changes in the concentration of a drug in the blood over time. Drugs will be given administered through the vein on Day 1 as well as through the skin on Days 2-3 because you are between the ages of 18-70 and are healthy.
- If you consent to participate, you will visit our laboratory 3 times for approximately 2 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. All study procedures will take place in the Spinal Cord Injury Research Laboratory of the Bronx VA Medical Center.

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

Inclusion Criteria:

• Male or female,
• Able-bodied
• Between the ages of 18-70 years old.

Exclusion Criteria:

• Previous adverse reaction or hypersensitivity to electrical stimulation,
• Known sensitivity to neostigmine or glycopyrrolate,

• History of mechanical obstruction of the GI or urinary tract,
• Myocardial infarction within 6 months of trial,
• Malignant and/or Uncontrollable Hypertension Defined by a blood pressure reading of 160/100 mmHg or higher with or without taking 3 or more different classes of anti-hypertensive medications,
• Organ damage or past failure (heart & kidney) and/or TIA-CVA as a result of hypertension,
• Known past history of coronary artery disease or bradyarrhythmia,
• Symptomatic orthostatic hypotension
• Deep brain stimulation
• Pregnancy (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 the study),
• Lactating, nursing females
• Inability to provide informed consent signaled by MoCA cognitive test score of 20 or less,
• History of ingrown hair folliculitis after shaving or epilation,
• Allergy to Sodium Lauryl Sulfate, Silver Chloride, Agarose Gel, Citric Acid, Isopropyl alcohol, Benzocaine or Polyethylene Glycol,
• Concurrent illness and fever,
• Concurrent participation in a research study.

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

- You will be asked to come to the SCI Research Laboratory (Room 7A-13, Bronx VA Medical Center) on the day of the scheduled appointment. Subjects will be asked to arrive at the Spinal Cord Research Center at the JJP VAMC (Room 7A-13) on the day of their appointment. On Day 1, following filling out paperwork and doing a brief assessment of your basic thinking abilities, we will insert an intravenous catheter into one of your larger veins and proceed to the restroom where we will measure your blood pressure, listen to the abdomen, measure vitals, draw blood, and ask about a couple of symptoms. Once you are ready, seated on the toilet and draped with a sheet, a doctor will start the administration of the two medications via the established intravenous catheter. The first day activities determine and confirm the levels of lower effective and safe intravenous doses of neostigmine and glycopyrrolate. You may have to defecate soon after receiving the two medications, the research personnel will vacate the restroom to afford you privacy and return when you summon them back. At that point you will have an opportunity to sit down onto a chair. We will draw blood 7 times out of the same catheter during the first hour after medication administration and freeze it after some processing. There will be two people in

the restroom with you. After an hour of observation and the seventh blood draw, the catheter will be withdrawn from your vein and you will be free to leave.

- The Iontophoresis devices we are using are called IBOX made by Dextronics and Hybresis made by Empi. Both of them are approved by the U.S. Food and Drug Administration for delivery of salts of drugs of which both neostigmine and glycopyrrolate are examples.
- During the second visit, at least 24 hours later, an intravenous catheter will be inserted into one of your larger veins. We will numb two skin areas on your legs sized 2x2 inches with a spray and pull the hair out quickly using a special machine. Two patches with separately-applied medications of neostigmine (0.07mg/kg) and glycopyrrolate (0.014mg/kg) are going to be used for systemic delivery. They are going to be connected to the IBOX with wires and Iontophoresis will proceed, delivering the medications simultaneously over a period of 20 minutes. The electric current passed through the skin will be very small, you can barely feel it. Once again we will draw blood 6 times. In the interim you will be sitting on the toilet until after you have a bowel movement. At that point you will have an opportunity to sit down onto a chair to wait out the remainder of the hour, at the end of which we will withdraw the intravenous catheter, you will take the gown off and will be free to leave the research center after scheduling another appointment.
- During the third and final visit, at least 24 hours following the second, the last intravenous catheter will be inserted into one of your larger veins after gowning-up. We will again numb the skin patch sized 2x2 inches with a spray and pull the hair out quickly using a special machine. You should not feel much pain at all. We will then proceed to the restroom where you will again sit down onto a toilet. A single wireless skin patch will be used for 20 minutes to deliver both the NEO and GLY together. We will draw blood 6 times and record your well-being for an hour after which we will remove the intravenous catheter. We will then finish filling out the payment forms, give you copies of all of the appropriate forms for your records and let you change back into your street clothes. This will conclude your participation and you will be free to leave the research center or to sign-up for another research study.
- 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 20 small vials blood is going to be collected and kept. In order to clear saline from tubing, 17 vials of 0.5mL of blood are going to be thrown into the incineration bin (to be burned at a later time). Throughout the 3 days of the experiment a total of no more than 80 mL or 6 tablespoons of blood will be taken from you.
- The experiment should last for no more than 6 hours, spread over 3 days, 3 IV catheters will be inserted and blood will be drawn from the vein a total of 37 times.

- Please note that the dose and concentration of NEO and GLY is greater for the Iontophoresis (through the skin) portion of the study (days 2 and 3) compared to day 1, where you receive the medication via IV (through the vein). However, transdermal (through the skin) administration of the medications is much slower and less efficient, and the surface area of the ION patch is relatively small. Thus, due to the different route of administration, you will effectively receive a similar amount of the medications as in the screening phase. This dose has been shown to be safe and effective in previous participants of related studies.
    - 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 days 2 and 3.

Intravenous Neostigmine and Glycopyrrolate (Day 1)
Drug Concentration and Dose
Neostigmine Methylsulfate Inj., USP 1mg/mL, 0.02mg/kg
Glycopyrrolate Inj., USP 0.2 mg/mL, 0.004mg/kg

Iontophoresis of Neostigmine and Glycopyrrolate (Days 2 and 3)
Drug Concentration and Dose
Neostigmine Methylsulfate, USP 5mg/mL solution; 0.07 mg/kg
Glycopyrrolate Inj., USP 1 mg/mL; 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.

TABLE OF STUDY EVENTS										
Time Points (in minutes)	**BL**	**0**	**2**	**4**	**7**	**10**	**20**	**30**	**40**	**60**
Start of NEO + GLY administration (IV or ION) is Time 0		x								
Blood Collection IV (2-3mL per vial) Day 1 Only	x		x	x	x	x	x		x	x
Blood Collection ION (2-3mL per vial) Day 2-3	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

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

- The small amount of electric current may cause a tingling sensation at the site of the electrode attachment for the first second on days 2 and 3.
- There will be a mild and transient pain during the hair removal over one 2X2 inch areas of the skin on days 2 and 3 of the experiment. The pain will be minimal as the skin-numbing medication (benzocaine spray) will be used prior to the hair removal on the anterior thigh and the removal will be done quickly.
- 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.
- 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.
- In case that we discover a major clinical finding during this experiment, we will notify your treating Physician and Dr. Cardozo, the Principal Investigator.

4. Expected Risks of Study:

- There is a small risk of ingrown hair in this study since the hair is removed by epilation. There is also a small risk of folliculitis (pimple at a hair follicle) at the site of an ingrown hair. 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.
- The risks of blood draw are: 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.
- To our knowledge, no bleeding or skin damage has ever been reported from the use of hair removal machines, such as the epilator we are going to be using, however, quick upward force is being applied to the hair shafts, so it is theoretically possible that bleeding may occur. Transient skin redness and pain are the most common side-effects.
- 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.
- 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.

5. Expected Benefits of the Study:

- You will help us advance our knowledge of skin permeability and how long the medications stay active once inside of the body. This new knowledge will be used to share with other scientists through publication of our findings for the public. We intend to develop a new method of delivering the two bowel-stimulating medications through the skin in the most effective, safe and convenient fashion possible.
- There may be no direct benefit to you from this study. But any information we get from this study will help others to control their incontinence and constipation.

6. Other Treatments Available:

- 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 we are currently investigating.

7. Use of Research Results:

- We will let you and your physician know of any important discoveries made during this study which may affect your willingness to participate in this study. All research materials generated from this study will remain in the possession of the James J. Peters VA Medical Center, under the supervision of Dr. Christopher Cardozo and his research team.
- Access to data will be restricted to the current research team members. All electronic data will be coded and stored on the VA network behind firewalls and in password-protected, access-restricted folders. All physical data such as case report forms and data collection sheets will be locked in a cabinet in a locked file room within the SCI Research Center at the James J. Peters VA Medical Center, and will not be removed from the facility. Your medical records will be maintained according to this medical center's requirements.
- Records will be retained according to National Archives and Records Administration, in accordance with Records Schedule RCS-10-1., Research Investigator Files and provide the planned practice for this study within the schedule requirements. 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 you may be reviewed by the following: Authorized representatives of the Bronx VAMC (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), and the Office for Human Research Protections (OHRP).
- Because this research involves articles regulated by the FDA, the FDA may choose to inspect and copy medical or research records that identify individual research subjects.
- A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. You can search this web site at any time.

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 will be reimbursed for your participation for this study as follows:

- If you complete the study partially, you will be reimbursed $60 for each day of participation. If you complete the study in its entirety, you will be reimbursed $180. You will receive payment within 8 weeks of the completion of the second set of iontophoresis.

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 x 1828], 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 inventors 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