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Real-Time Levodopa Level Monitoring in Parkinson Disease

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University of California, San Diego
Consent to Act as a Research Subject

Real-Time Biosensor-Based Monitoring of Levodopa Levels in Parkinson Disease (PD): Experiment 3, Phase II.1 (Validation of Capillary Blood Sensor in People with PD)

Introduction

Dr. Irene Litvan and Dr. Joseph Wang and associates are conducting this research and asking for your consent to participate. This section provides a summary of important information. The rest of the form provides additional details.

- Research is voluntary - whether or not you join is your decision. You can discuss your decision with others (such as family, friends, or another physician).
- You can say yes but change your mind later.
- If you say no, we will not hold your decision against you.
- Your decision will not affect your health care or any other benefits you may be entitled to.
- You can say no even if the person inviting you is part of your healthcare team.
- Please ask questions or mention concerns before, during or after the research.

The researchers are trying to find out whether a new device using fingerstick blood -based sensory technology is safe, acceptable to users, and able to detect levodopa levels in people with Parkinson disease (PD). This experiment will not influence or change your levodopa treatment or improve management of your PD. You have been asked to participate in this study because you have been diagnosed with PD and you are taking carbidopa/levodopa. Participation in this study may or may not benefit you directly and may result in new knowledge that can help others in the future.

You will first undergo several procedures to determine if you are eligible for the study. If you are eligible, you will attend one study visit. During the study visit, you will visit the clinic once for about 4 hours.

The most commonly expected risks of the study are temporary side effects from taking levodopa, including temporary nausea and involuntary movements (dyskinesias), and side effects from holding levodopa before study procedures which may cause temporary worsening of parkinsonian symptoms.

The most serious risks of the study may include temporary psychiatric side effects from levodopa (such as hallucinations, delusions, or mood changes), which are uncommon, and neuroleptic malignant syndrome from holding levodopa, which is very rare.

Additional, detailed information about this research is provided below. Please feel free to ask questions before signing this consent.

Why have you been asked to participate, how you were selected, and what is the approximate number of participants in the study?
You have been asked to participate in this study because you have PD. There will be approximately 40 participants recruited and 20 participants included at this site for the Phase II.1 experiment. Five healthy volunteers and 20 participants with PD will be included in the other phases of this experiment.

What will happen to you in this study and which procedures are standard of care and which are experimental?
If you agree to be in this study, you will attend two visits: a screening visit and a study visit. None of the procedures that will be performed as part of this study are for your health care, and all tests and procedures done in this study are for research only.

During the screening visit:
You will review the protocol and informed consent forms with Dr. Litvan or Dr. Longardner and clinical coordinator. If you agree to participate, Dr. Longardner or Dr. Litvan will gather information and perform a physical exam to confirm your eligibility for the study. Nursing staff will measure your blood pressure. You will also undergo a brief cognitive assessment. If you are found to be eligible, you will be asked to attend a study visit.

During the study visit:
You will be asked to hold (i.e., not take) your home medications for treating PD for at least 10 hours before the study visit and throughout the day during the study procedures (you will take your last levodopa dose the night before the study visit). You will also be asked to abstain from caffeine and meals containing protein (e.g., including fish and poultry, eggs, meats, tofu, and dairy products such as milk, cheese, or yogurt on the morning of the visit), since this may interfere with measuring blood levels of levodopa.

A low-protein breakfast will be provided on the morning of the study visit. A movement disorders specialist will characterize your baseline motor symptoms in the "off" state by performing a focused neurologic examination. A nurse will place one intravenous (IV) catheter in your arm. This IV catheter will be used to collect blood samples at certain intervals, which will later be sent to a lab to measure levodopa levels.

During the visit, we will give you one oral dose of instant release carbidopa/levodopa tablet, which is swallowed whole. This dose will be the same amount of levodopa that you are taking at home, combined with carbidopa in a 1:4 ratio (e.g., 50mg carbidopa/200mg levodopa). Carbidopa/levodopa is most commonly prescribed in a 1:4 ratio. A movement disorders neurologist will monitor for side effects by observing your vital signs, movements, and behavior. If side effects are mild, they will be noted and the study will proceed. If the side effects are severe, the study will be stopped.

We will check your levodopa level throughout the visit using the fingerstick blood-based sensor strip. This sensor is an investigational device that is not approved by the FDA. However, similar devices are being commonly used for diabetic patients to monitor blood glucose levels. We will do a fingerstick blood draw (i.e., puncturing the skin on the tip of one of your fingers using a

small sharp lancet to draw blood) before taking carbidopa/levodopa and will then repeat the fingerstick blood draw every 10 minutes for a total of up to 90 minutes (11 total fingerstick blood draws). The amount of blood drawn from each fingerstick puncture will be several drops (total blood collected from fingerstick blood draws will be less than 1mL (less than ¼ teaspoon). Throughout the visit, we will also draw your blood through the vein to measure the level of levodopa at the same times as the fingerstick blood draw. We will insert an intravenous (IV) catheter in your arm and will extract about than 1 ml (less than ¼ teaspoon) of blood before you take the levodopa, and another 1 mL of blood every 10 minutes for a total of up to 90 minutes after taking carbidopa/levodopa. The total amount of blood extracted from your vein will be about 11 ml of blood (total about two teaspoons). We will remove the IV catheter at the end of the visit.

We will measure levodopa levels using the capillary blood sensor at the same time as each venous blood collection. Venous blood samples will be labeled with a unique identifying code that does not contain any personal health information, and the collection time. After the study visit concludes, we will send venous blood samples all together to a local laboratory for HPLC analysis, which will be used as a "gold standard" comparison for levodopa measurements obtained using the capillary blood test strip sensor. “Gold standard” means that this is the test currently accepted in the medical community as giving accurate results that can be used to make treatment decision. Because this test is expensive and time-consuming, the researchers are looking for ways to measure levodopa that are faster and cheaper, like this capillary blood sensor.

Throughout the visit, a movement disorders neurologist will evaluate your PD motor symptoms repeatedly along with the repeated levodopa measurements. You will also do finger tapping tasks at the same intervals as levodopa measurements described above. You will be asked to complete questionnaires about your non-motor symptoms and will also undergo a cognitive test. At the end of the visit, we will ask you to rate the acceptability of the levodopa sensor device using a scale.

Table 1: Experiment 3 Phase II.1 Study Visit Schedule

Procedure	**Time**
-Arrival, low-protein breakfast	7:30-8:00am
Baseline motor evaluations in the “off” state:	8:00-8:30am
-Placement of IV catheter[2]	8:30-8:45am
-Baseline venous blood collection[2] -Fingerstick blood draw[1] and baseline capillary blood sensor reading (< 1 minute)[3]	Repeated every 10 minutes (10 minutes before taking levodopa and at the time of taking levodopa) 8:45am-8:55
-Oral carbidopa/levodopa administration in 1:4 ratio[2]	8:55am
-Finger tapping quantitative measurement[2] (Total duration = 1 minute)	Repeated every 10 minutes from 8:55am-10:25am (90 minutes total)

-Venous blood collection for HPLC analysis (< 1 minute)[2] -Fingerstick[2] and capillary blood sensory reading (~ 1 minute)[3]	Repeated every 10 minutes from 8:55am-10:25am (90 minutes total)
- Brief motor symptom assessment[1] - Vital sign assessment (1 minute)[2]	Repeated every 30 minutes from 9:25am-10:25am
- Removal of IV catheter[2]	10:25am-10:30am
-Cognitive assessment[4]	10:30am-10:45am
-Non-motor symptom questionnaires[1]	10:45am-11:05am
-Motor symptom questionnaires[1]	11:05am-11:25am
-Acceptability rating of capillary blood biosensor (Likert-style questionnaire)[4]	Once at 11:30am
- Departure	11:30am-11:45am
Study procedures 1. Performed by Dr. Longardner or Dr. Litvan 2. Performed by nursing staff 3. Performed by bioengineering research fellow 4. Performed by clinical research coordinator	

How much time will each study procedure take and how long will the study last?
Your participation will involve two visits: (1) a screening visit and (2) a study visit. This screening visit will last 2-2.5 hours. The study visit will last about 4 hours.

What risks are associated with this study?
Participation in this study may involve some risks or discomforts. In addition to the risks described at the beginning of this form,

1. **Risks of Withholding Caffeine**
Participants will be asked to abstain from caffeine on the day of the study visit (the second visit, after you have completed the screening visit), as this may interfere with blood levodopa level analysis. In people who are accustomed to regular caffeine consumption, holding caffeine may result in mild temporary withdrawal symptoms including headache, mood changes, irritability, tiredness, etc.

2. Risk of IV Catheter Placement
There is risk associated with placement of IV catheters in the arms, including local discomfort and bruising, and a low risk of infection, as skin will be properly cleaned prior to insertion. The IV catheter will be placed by trained nursing staff and will be removed at the end of the visit.

3. Risk of IV Blood Collection
There is risk from IV blood collection, which will be drawn from an IV catheter placed by research clinic nursing staff. Owing to the small volumes of blood samples required (approximately 1 mL per sample, total 11 mL, which is equivalent to about 2 teaspoons), there is minimal risk of excessive blood loss.

4. Risk of the Capillary Blood Sensor Device
The fingerstick lancets used to draw capillary blood will likely cause temporary pain or discomfort at the fingertip during each brief puncture. These fingertip punctures have a low risk of infection. There is low risk of bleeding, as the amount of blood collected from each finger stick is several drops at most, less than one milliliter (less than 1/4 teaspoon). This is the same type of equipment and same type of procedure that is routinely used by people with diabetes to measure blood glucose at home using a glucometer.

5. Risk of Oral Carbidopa Administration
Carbidopa is one of the substances (the other is levodopa) in the pill that you will take. It is used to reduce the side effects of the levodopa, like nausea, and to make it easier for the brain to absorb the levodopa. Carbidopa by itself has no benefit or side effects. Allergic reaction to oral carbidopa is very rare. All PD patients recruited will already be taking carbidopa in combination with levodopa as part of their home regimen, so there will be no risk of an unknown allergic reaction occurring in PD patients.

6. Risk of Oral Levodopa Administration:
Levodopa is the other substance in the pill that you will take. Any side effects may last up to several hours from the dose and frequency of levodopa used in this study. The most common adverse reactions are nausea and involuntary movements (dyskinesias). You have been using levodopa, so you are likely already familiar with the side effects.

The following other adverse reactions from oral carbidopa/levodopa instant release have been reported but are very unlikely (organized by organ system):

General: chest pain, generalized pain; fatigue
Cardiovascular: heart rhythm irregularities, low blood pressure, high blood pressure, fainting, vein inflammation, palpitations, heart attack
Gastrointestinal: dark saliva, bleeding from stomach or intestines, development of intestinal ulcer, decrease appetite, vomiting, diarrhea, constipation, indigestion, dry mouth, changes in taste; abdominal pain, trouble swallowing, excessive saliva, flatulence (gas), clenching teeth, burning tongue, hiccups, heartburn
Hematologic: low counts of red blood cells, white blood cells, and platelets
Hypersensitivity: swelling, hives, itching, rash, blistering
Metabolic: edema, weight gain, weight loss
Musculoskeletal: leg pain, back pain, shoulder pain, muscle cramps.
Nervous System/Psychiatric: psychotic episodes including delusions, hallucinations, and paranoid ideation, neuroleptic malignant syndrome (a rare syndrome including symptoms of fever, worsening muscle rigidity, altered mentation), episodes of slowness ("on-off" phenomenon – re-emergence of PD symptoms as the medication's effect decreases), confusion,

agitation, dizziness, sleepiness, dream abnormalities including nightmares, insomnia, tingling sensation, headache, depression with or without development of suicidal tendencies, dementia, pathological gambling, increased libido including hypersexuality, impulse control symptoms, incoordination, abnormal movements, falling, anxiety, gait changes, nervousness, decreased mental acuity, memory impairment, disorientation, euphoria, involuntary blinking or jaw clenching, increased tremor, numbness, muscle twitching, activation of latent Horner's syndrome, peripheral neuropathy
Respiratory: difficulty breathing, upper respiratory infection, throat pain, cough
Skin: rash, increased sweating, hair loss, dark sweat, malignant melanoma (skin cancer), flushing
Special senses: involuntary eye movements, diplopia (double vision), blurred vision, dilated pupils
Urogenital: urinary tract infection, frequent urination, dark urine, prolonged erection, urine retention, loss of bladder control (incontinence)
Miscellaneous: unusual breathing patterns, faintness, hoarseness, feeling unwell (malaise), hot flashes, sense of stimulation

7. Risks of Withholding PD Medications
You will be asked to hold (i.e., not take) your PD medications for 10 hours prior to the study visit and during the study visit. This may result in temporary worsening of your PD symptoms (e.g. tremor, muscle rigidity, movement speed, walking problems, anxiety, etc.), which may be uncomfortable. Evaluation off PD medications is routinely performed for research, and this experience is similar to the symptom fluctuations that people with PD may experience in daily life if the medication wears off. Therefore, you are strongly encouraged to attend the visit with a caregiver.

Sporadic cases of a very rare but life-threatening problem called neuroleptic malignant syndrome have been reported with reducing or stopping levodopa in PD. This syndrome causes fever, worse muscle stiffness, involuntary movements, confusion, behavior changes, or drowsiness, autonomic disturbances (e.g., changes in blood pressure or heart rate), and blood laboratory changes.

8. Risk of Loss of Confidentiality
Participating in this study involves a potential risk of loss of confidentiality. Data collected from this study will be kept confidential to the extent allowed by law. There are measures in place to minimize this risk.

Because this is a research study, there may be some unknown risks that are currently unforeseeable. You will be informed of any significant new findings.

Are there risks to the reproductive system or a developing fetus?
The effects of the treatment procedures including levodopa may pose some unforeseeable risks on the developing fetus. For this reason, participants in this investigational study should not be pregnant.

After you have been enrolled in this study and during the research, pregnancy testing will be performed. If you have a positive pregnancy test, we may withdraw you from the study. If you

become pregnant or if there is any chance of pregnancy (e.g., late menstrual period), please contact the study personnel immediately so that we may provide medical assistance and counseling.

What are the alternatives to participating in this study?
The alternative to participation in this study is not to participate.

What benefits can be reasonably expected?
This study does not offer any direct benefit to you, but the study may result in more knowledge about monitoring levodopa and treatment of PD. No medical care will be provided during and beyond the completion of the study, with the exception when new diagnostic information arises during this study, and in the unlikely event of study-related adverse events. You and/or your insurance will be responsible for treating your condition.

You will remain under the care of your own clinician(s) throughout the study. During the study and following study completion or withdrawal from the study, any information relevant to your health care will be discussed with you and your treating clinician(s).

What happens if you change your mind about participating?
If you decide that you no longer wish to continue in this study, you will be requested to: notify the clinical coordinator by email or phone call.

You will be told if any important new information is found during the course of this study that may affect your wanting to continue.

Can you be withdrawn from the study without your consent?
You may be withdrawn from the study for the following reasons:

1. You experience any severe adverse events
2. Dr. Litvan or Dr Longardner believes that it is in your best medical interest

You may also be withdrawn from the study if you do not follow the instructions given you by the study personnel.

Will you be compensated for participating in this study?
There will be no compensation for your participation in this study.

Are there any costs associated with participating in this study?
There will be no cost to you for participating in this study.

What if you are injured as a direct result of being in this study?
If you are injured as a direct result of participation in this research, the University of California will provide any medical care you need to treat those injuries. The University will not provide any other form of compensation to you if you are injured. You may call the Human Research Protections Program Office at 858-246-HRPP (858-246-4777) for more information about this, to inquire about your rights as a research subject or to report research-related problems.

What about your confidentiality?
Research records will be kept confidential to the extent allowed by law. Electronic information will be stored on a password-protected server in a secure database. You will be assigned a code number. This code number will be used on study information instead of information that may identify you. Research related papers will be kept in a locked cabinet in the Neurosciences workspace. Only the study staff can link the code back to you. Research records may be reviewed by the UCSD Institutional Review Board and the National Institutes of Health.

This research is covered by a Certificate of Confidentiality from The National Institutes of Health. Researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research *unless* there is a federal, state, or local law that requires disclosure (such as to report child abuse, elder abuse, intent to hurt self or others, or communicable diseases), you have consented to the disclosure, including for your medical treatment; or it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the NIH which is funding the project or for information that must be disclosed in order to meet the requirements of the Food and Drug Administration (FDA). You should also understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the research to release it.

The information or biospecimens collected as part of the research, even if personal identifiers are removed, will not be used or distributed for future research studies.

Biospecimens (such as blood, tissue, or saliva) collected from you for this study and/or information obtained from your biospecimens may be used in this research or other research and shared with other organizations. You will not share in any commercial value or profit derived from the use of your biospecimens and/or information obtained from them.

A description of this clinical trial will be available on http://www.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.

Under California law, we must report information about known or reasonably suspected incidents of abuse or neglect of a child, dependent adult or elder including physical, sexual, emotional, and financial abuse or neglect. If any investigator has or is given such information, he or she may be required to report such information to the appropriate authorities.

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Will you receive any results from participating in this study?
The results from your participation in this study will not be shared with you.

Who can you call if you have questions?
This study has been explained to you and your questions have been answered. If you have other questions or research-related problems, you may reach Dr. Litvan at (858) 822-5871 or Dr. Longardner at (858) 246-2579.

You may call the Human Research Protections Program Office at 858-246-HRPP (858-246-4777) to inquire about your rights as a research subject or to report research-related problems.

Your Signature and Consent
You have received a copy of this consent document and a copy of the "Experimental Subject's Bill of Rights" to keep.

You agree to participate.

_____	_____
Subject's signature	Date
_____	_____
Signature of the person conducting the informed consent discussion	Date