Intergenerational transmission of sucralose and acesulfame-potassium from mothers to their infants via human milk: a pharmacokinetic study

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RESEARCH PROTOCOL

TITLE: Intergenerational Transmission of Low-calorie Sweeteners in Breast Milk

RESEARCH PLAN

A. Specific Aims

Aim 1: Determine the pharmacokinetics of sucralose and ace-K in mothers' breast milk and plasma after ingestion of a commercially-available diet beverage containing sucralose and ace-K.

Hypothesis 1: We hypothesize that ace-K will be rapidly transferred into breast milk, with peak concentrations measured within 1 hour of diet soda ingestion. We further hypothesize that sucralose will appear in the breast milk approximately 2 hours after ingestion, with peak concentrations detected approximately 8 hours later.

Aim 2: Assess the pharmacokinetics of sucralose and ace-K in exclusively breastfeeding infants following maternal ingestion of commercially-available diet beverage containing sucralose and ace-K.

Hypothesis 2: We hypothesize that sucralose and ace-K concentrations in infants' plasma will be proportional to concentrations measured in their mothers' breast milk.

B. Background and Significance

Low-calorie sweeteners (LCS), including sucralose and acesulfame-potassium (ace-K), provide sweetness without calories, and beverages with LCS are consumed by 44% of lactating women in the United States. The number of consumer products containing LCS has increased four-fold in recent years, and this trend will likely continue with ongoing public health efforts to reduce added sugars. Due to their chemical and physical properties, sucralose and ace-K are found widely in foods and beverages, often in combination. Yet, most consumers are unaware of their presence in a diverse array of products (e.g. non-diet fruit drinks, such as Hawaiian Punch™, no sugar added ice cream, "high-fiber" oatmeal, Carb Smart bread™) in addition to diet beverages. Neither sucralose nor ace-K are metabolized;[3] and thus, both are detectable in biological fluids, including human breast milk. However, the current understanding of LCS effects on diet, weight, and health, especially when exposure begins early in life, is extremely limited.

We have previously demonstrated that sucralose and ace-K are present in human breast milk and are ingested by nursing infants. Sucralose and ace-K have undergone extensive safety evaluations and are approved by the US Food and Drug Administration (FDA) as food additives and by numerous other regulatory bodies worldwide. While their safety is well-established from a toxicological perspective, sucralose and ace-K elicit striking metabolic effects, and accumulating epidemiologic

and mechanistic evidence demonstrates that early life LCS exposure may adversely impact future cardiometabolic disease risk.

Given that early exposures impact later development of cardiometabolic disease, sucralose and ace-K exposure via the breast milk may adversely impact developmental programming of cardiometabolic risk, through mechanisms including potential alteration of infants' taste preferences, appetite, and/or gut microbiome composition. The purpose of this study is to measure sucralose and ace-K in maternal breast milk and plasma at pre-specified, serial, time-points for 72 hours, as well as in a sample of infants' plasma. This will serve as a critical step towards our long-term goal of elucidating effects of early life LCS exposure on infants' future diet, weight, and health.

C. Preliminary Studies

The PI is Allison C. Sylvetsky Ph.D., an Assistant Professor in the Department of Exercise and Nutrition Sciences at the George Washington University (GW). Dr. Sylvetsky is a nutrition scientist with a research focus on the role of LCS in diet, weight, and cardiometabolic health. Dr. Sylvetsky has nearly ten years of experience studying LCS and over five years of experience studying LCS exposure via breast milk. Dr. Sylvetsky has led and/or contributed to two prior studies involving human breast milk collection, referenced below:

1. **Sylvetsky AC**, Gardner AL, Bauman V, Blau JE, Garraffo HM, Walter PJ & Rother KI. Nonnutritive sweeteners in breast milk. *Journal of Toxicology and Environmental Health A*. 2015; 78 (16): 1029-32.

2. Rother KI, **Sylvetsky AC**, Walter PJ, Garraffo HM, Demarath EW, Fields DA. Pharmacokinetics of Sucralose and Acesulfame-potassium in Breast Milk Following Ingestion of Diet Soda. *J Pediatr Gastroenterol* 2018 Mar;66(3):466-470. PMID: 29077645

Jeanne Murphy, Ph.D., C.N.M, co-investigator, is an Assistant Professor in the GW School of Nursing and has extensive experience recruiting and enrolling women in biomedical research studies. Dr. Murphy is also a clinical midwife at the GW Midwifery Practice within the Department of Obstetrics and Gynecology at the GW School of Medicine and Health Sciences, and has regular contact with a large volume of breastfeeding mothers.

Dr. Sylvetsky and Dr. Murphy have recently collaborated on an analysis of low-calorie sweetener intake among lactating women using data collected from 1,422 lactating women in the Infant Feeding Practices Study II (IFPSII). In this sample, 44% of lactating mothers reported consumption of LCS-containing beverages in 2005-2007, 18% of whom reported consumption once per day. A manuscript reporting these findings has been submitted and is currently under review:

1. Huang Q, **Murphy J**, Smith ER, **Sylvetsky AC**. Diet beverage intake during lactation and associations with maternal and infant outcomes in the Infant Feeding Practices II Study [under review, Journal of Pediatric Gastroenterology and Nutrition].

D. Research Design and Methods

Mother-infant dyads will be recruited from the GW Midwifery Service, a division within the GW School of Medicine and Health Sciences (GWSMHS). Eligibility will be assessed during a phone screening, after which, eligible mothers will schedule a Zoom enrollment visit, and will subsequently be scheduled for a study visit approximately one week later, which will be 9 hours in duration.

During the enrollment visit (remote via Zoom), participants will provide electronic consent, after which demographic data will be collected, and mothers will be provided with instructions for completing an online, photo-assisted, 7-day food record for 7 days prior to their in-person study visit. At the end of the Zoom™ visit, the in-person visit, to take place at Children's National Hospital, will be scheduled for approximately one week later.

During the week prior to their scheduled study visit, mothers will be instructed to avoid all products containing low-calorie sweeteners (and will be given a list of specific products to avoid) and to complete an online, photo-assisted, 7-day food record.

The study will take place in Clinical Research Unit (CRU) at Children's National Hospital and will last for approximately 9 hours, to provide sufficient time for baseline assessments and 8 hours of supervised sample collection following ingestion of a sucralose and ace-K containing diet beverage.

Written informed consent will be obtained at the start of the in-person visit, after which a brief medical history, and stage of lactation will be collected, and maternal height and weight will be measured. You will also be asked questions about other factors that may impact sucralose and ace-K pharmacokinetics, including smoking, alcohol intake, concomitant medications, and time since last feed will be collected. Infant anthropometric and birth data including length, weight, head circumference, birth order, sex, gestational age and the presence of any known health conditions will be collected via the mother's report. Mothers will also be asked to complete a questionnaire asking about the type of advice, if any, given to them about LCS use during lactation, as well as the amount and types of LCS-containing foods and beverages consumed since initiation of breastfeeding.

A breast milk sample (10 mL) will be collected from the mother for assessment of baseline sucralose and ace-K concentrations. The mother will then have an intravenous catheter (IV) placed by a trained phlebotomist in an antecubital vein, while in the recumbent position, after which, a baseline plasma sample (6 mL) will be collected.

After collection of a baseline plasma sample, mothers will be asked to drink 24 ounces of a commercially-available sucralose and ace-K sweetened diet beverage (hereafter diet beverage), containing a total of approximately 140 mg of sucralose and 85 mg of ace-K, within 10 minutes, prior to a standardized, LCS-free, breakfast meal consisting of a pre-packaged breakfast sandwich and fruit. These concentrations reflect the amount of sucralose and ace-K in two 12-ounce cans of a commercially-available, sucralose and ace-K sweetened diet soda, such as Diet Pepsi™ and corresponds to approximately 2

mg/kg sucralose and 1.15 mg/kg/day ace-K for a 70 kg adult, well below the acceptable daily intakes (ADI) 5 mg/kg and 15 mg/kg for sucralose and ace-K, respectively.

After ingestion of the diet beverage, mothers will remain at the CRU for eight hours and will provide a plasma sample 0.5, 1, 1.5, 2, 3, 4, 6, 8 hours (6 mL at each timepoint) following diet beverage ingestion and a breast milk sample 1, 2, 3, 4, 6, 8, 12 hours following diet beverage ingestion (10 mL at each timepoint).

A plasma sample (100 µL) will be collected from each infant at one of the following prespecified time intervals following maternal ingestion of the LCS containing beverage: 1.5-3 hours, 3-5 hours, 5-7 hours, 7-9 hours, and 9-14 hours. The infant sampling approach is designed to capture the timeframes when maternal breast milk concentrations for ace-K and sucralose will be at their maximum levels, while collecting only a single plasma sample from each infant to minimize risk. Infants' plasma will be collected via heel stick to reduce pain and minimize risk. Heel sticks are the most common way to collect infants' blood and are appropriate for most babies, including premature infants, neonates, and babies <6 months old. Heel sampling will be conducted by trained nursing staff in the CRU.

Breast milk samples will be immediately frozen at -20°C and transferred to a -80°C freezer at the end of each visit for long-term storage. Blood samples will be centrifuged at 4°C and the plasma stored at -80°C until analysis.

After collection of plasma and breast milk samples at the 8-hour timepoint (described above) mother-infant dyads will return home. The mother will be asked to collect the 12hour breast milk sample at home and bring it to the hospital the following day. Additionally, the mother will be asked to complete a 3-day online, photo-assisted food record for the next three days and to continue to avoid products with LCS. The mother will be asked to return to the clinic between 7AM-9AM on these following three consecutive days (24, 48, and 72 hours after diet beverage ingestion) to provide a blood sample (6 mL each day) by a venous blood draw by a trained phlebotomist and to provide a breast milk sample (10 mL, 24-hour time point only). The total amount of blood collected from mothers over the course of the study (9-hour long study visit, and sample on three consecutive days) will be 72 mL. The total amount of breast milk collected from mothers over the course of the study (9-hour long study visit and 24-hour sample) will be 90 mL. The infant will provide a single blood sample, for a total of 100 µL collected over the course of the study.

E. Study Population:

We plan to study 50 lactating mothers and their infants, for a total of 100 participants. Eligibility will be assessed during a phone screening. For eligibility, mothers will have given birth within the past 6 months, be ≥18 years of age, and be exclusively breastfeeding. We will limit enrollment to mothers of infants <6 months of age, consistent with recommendations to introduce solid foods. Any individual with a known allergy or contraindication to LCS will be excluded. Only mothers whose infants are ≥4 weeks

corrected age will be eligible. Any mothers or infants with an active nutritional disorder known to cause malabsorption will be excluded.

Planned distribution by sex: We will recruit lactating women and their infants. All mothers (n=50) will therefore be female. However, we will recruit infants irrespective of their sex and therefore anticipate that approximately half (n=25) of the total sample of infants (n=50) will consist of females and half (n=25) will consist of males.

- Rationale: This research topic pertains specifically to lactating women because this study aims to measure low-calorie sweetener concentrations in the breast milk. However, findings will pertain to both males and female infants and therefore both boys and girls will be included

Planned distribution by race/ethnicity: Mother-infant dyads will be recruited without bias to race or ethnicity, and eligibility for inclusion within the study will not be determined by these factors. We anticipate the demographic profile of participants will be proportional to the race/ethnic distribution of mothers seen at The GW Midwifery Service.

F. Human Subjects

All of the data collected in this study are collected specifically for research purposes. Data will be provided through self-report of the mother (demographic information, habitual lowcalorie sweetener consumption, infant anthropometry etc.) and collected of biospecimens, including blood and breast milk, as well as measurement of maternal height and weight in the Clinical Research Unit.

1. Participant recruitment: Mother-infant dyads will be recruited from the waiting room of the GW Midwifery Service, a division within the GW School of Medicine and Health Sciences, where co-investigator Dr. Murphy is a practicing nurse midwife. We will also recruit using provider referral (from providers at GW Midwifery Clinic, including Dr. Murphy), word of mouth, social media, and through circulating recruitment flyers and study information via local community organization list-serves.

2. Consent process: Mothers will attend a private webinar (approximately 30 minutes, held via Zoom with a research team member, parent, and their child), during which electronic informed consent will be obtained. Electronic consent will be obtained because this first study visit will take place entirely online (via Zoom). A study team member will explain the study to the mother and will first go over the electronic consent form with them. Mothers will be asked to read and review the consent form. All mothers will receive a verbal lay explanation of the purposes, procedures, and potential risks of the study and of their rights as research participants. Mothers will be given the opportunity to discuss the study with their friends and family members prior to agreeing to participate. The parent will be reminded that they may withdraw consent at any time throughout the course of the study. The mother will have the opportunity to ask any questions before electronically signing the form. Written consent will then be obtained at the start of the

in-person study visit, approximately one week later, prior to beginning any of the in-person study procedures such as collection of breast milk and blood samples.

3. Compensation provided: Compensation of up to $400 will be provided. This includes $25 for completion of the Zoom visit, $25 for completion of the photo-assisted food records, $200 for the 9-hour in-person study visit, and $50 per sample obtained at 24, 48, and 72 hours (three consecutive mornings after study visit). Additional compensation will be provided to cover the cost of transportation to/from study and/or parking on each day of the study (9 hour visit and sample collection on three subsequent days). Participants will also be provided with a small study branded gift bag (estimated $30 value) containing a small handheld breast pump, cooler bag, and a onesie for the infant.

G. Risks and Side Effects:

- The study procedures and the potential risks associated with each are described below.
    - General: study participation requires compliance with study procedures for up to 4 days. Some individuals may find the time required to complete the study procedures to be an inconvenience in their routine life.
    - We do not anticipate any long-term risks to participants from participation in this study. However, there is always the possibility of risks currently unknown and the potential breach of privacy.
        - To minimize the risk of breach of confidentiality, all data will be immediately de-identified following collection. Data will initially be associated with an alphanumeric code and a copy of the key to this code will be kept in a locked filing cabinet. All computers used for analysis of this data are password protected and kept in locked offices and/or laboratories.
    - Blood Draws: Although blood draws are a standard medical procedure, there is a risk of discomfort at the site of the needle entry or bruising at the site. There is also a remote risk of fainting or local infection associated with drawing blood.
        - To minimize risk associated with blood draws, only trained phlebotomy staff in the Clinical Research Unit at Children's National, will carry out these procedures. Furthermore, we will collect blood samples from infants via heel stick to minimize pain and reduce the invasiveness of the procedure.
- Mothers will be made aware that study participation is entirely voluntary and will have the opportunity to choose not to participate. Mothers and their infant will have the opportunity to drop out of the study at any time.

Our assessment of risk does not preclude the potential for unanticipated adverse events, serious or otherwise, since it is not always possible to predict with certainty the absolute risk involved for any given individual. Therefore, we plan to monitor the data and the safety of the study as follows:

- An adverse event (AE) is any untoward medical occurrence in a subject undergoing a study-related procedure and believed reasonably to be caused by a study-related procedure. An adverse event in our study could involve a sign, symptom, abnormal laboratory value or vital sign, and any combination of these.

- Each mother-infant dyad will be evaluated for adverse events through examination a continued telephone contact with participants throughout the entire study.

- The possibility of adverse events will be monitored for each mother and infant and will be attributed to the study procedures/design by the PI and collaborator Dr. Van Den Anker MD (who is a neonatologist and pediatric pharmacologist at Children's National Hospital, please see letter enclosed), according to the following categories:

    - a. Definite: Adverse event(s) will clearly be related to the intervention or study procedures.
    - b. Probable: Adverse event(s) will likely be related to the intervention or study procedures.
    - c. Possible: Adverse event(s) may be related to the intervention or study procedures.
    - d. Unlikely: Adverse event(s) will doubtfully be related to the intervention or study procedures.
    - e. Unrelated: Adverse event(s) will clearly not be related to the intervention or study procedures.
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  o The following scale will be used in grading the severity of any adverse events noted during this study:

  1 No adverse event or within normal limits
  2 Mild adverse event
  3 Moderate adverse event
  4 Severe adverse event resulting in hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect
  5 Life-threatening or disabling adverse event 6 Fatal adverse event.

Serious unanticipated events will be reported within 24 hours to the IRB at GW and at CNH. Adverse events will be considered serious if graded 3 or higher on the scale outlined above. An adverse event report including a description of the event, when the event occurred, and when and how the event was reported, will be generated for each event. Any documentation related to the event, or its attribution will be included in the report.

The PI (Dr. Sylvetsky) will conduct a review of adverse events upon completion of every mother-infant dyad. She will evaluate the frequency and severity of the adverse event(s) and, in conjunction with Dr. Van den Anker and the IRB, will determine if modifications to the protocol or consent forms are required. A report to the IRB will be made at a minimum of once every 6 months, including when re-approval for the protocol is sought.

H. Benefits:

There are no direct benefits associated with participation in this study. However, the potential public health benefits of this study are of substantial magnitude. The consumption of LCS is widespread, including among lactating women, yet effects of early life LCS exposure are not well understood.

I. Outside Consultants/Collaborators

Please see Appendix.

J. Contractual Agreements

Not applicable.

K. Costs To Subjects:

There are no costs to participants associated with taking part in this study.

L. Conflicts Of Interest:

The investigators have no conflicts of interest to disclose.

M. Confidentiality:

Each participant will be assigned a study ID number, which will be coded to include the number 21 in front of individual subject numbers (Ex: subject #1 will be 2101, subject #14 will be 2114) which is necessary to protect the confidentiality of the subjects' participation in the study. The link between study code numbers and direct identifiers (name, email, phone number) will be kept in the password-protected, spreadsheet by the PI Dr. Sylvetsky and stored separately from the study data entered into REDCap. Only coded data will be exported from REDCap and used for data analysis.

All meetings and webinars will take place in a private (physical or virtual) room to ensure the participant's privacy. The study participant's contact information will be securely stored electronically for internal use during the study. At the end of the study, all research records will be stored in a secure (password protected electronic or locked file cabinet) location for the time period dictated by the sponsor and institutional regulations. The research data will not include the participant's identifying information. The study data entry and study management systems used by research staff will be secured and password protected. All research team members will have completed appropriate human subjects training and will undergo protocol specific training.

N. Subject Compensation:

Each mother-infant dyad will receive compensation of up to $400. This includes $25 for completion of the Zoom visit, $25 for completion of the photo-assisted food records, $200 for the 9-hour in-person study visit, and $50 per sample obtained at 24, 48, and 72 hours (three consecutive mornings after study visit). The Forte Participant Payment System will be used to manage payments to research participants. Additional compensation will be provided to cover the cost of transportation to/from study and/or parking on each day of the study (9 hour visit and sample collection on three subsequent days). Participants will also be provided with a small study branded gift bag (estimated $30 value) containing a small handheld breast pump, cooler bag, and a onesie for the infant.

O. Facilities and Equipment

All procedures will be conducted either remotely via Zoom or in the Clinical Research Unit at Children's National Hospital. The Clinical Research Unit is designed for conduct of research with infants and children and has existing staff, facilities, and resources that will be used for this project. This includes trained pediatric research nurses and phlebotomists, laboratory processing staff and facilities, and short- and long-term sample storage and biorepository services.

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