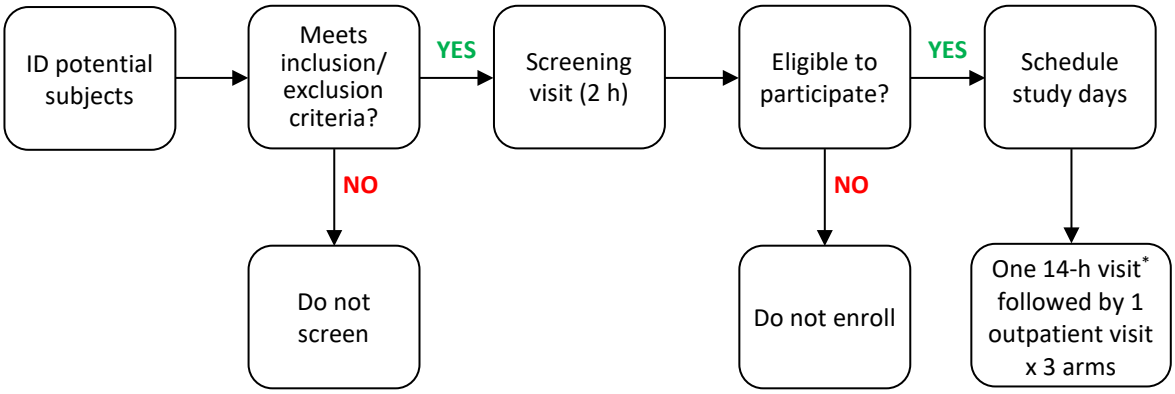
CLINICAL EVALUATION OF THE PHARMACOKINETIC GOLDENSEAL-METFORMIN INTERACTION IN DIABETIC PATIENTS

NCT05081583

MAY 29, 2024

STUDY PROCEDURES FLOWCHART

Figure 1. *Overview of procedures*.



*Preceded by 27-day exposure to goldenseal for Arm 3

SUBJECTS

Well-controlled diabetic adult volunteers (10 men and 10 non-pregnant, non-lactating women), aged from 18-65 years, of any race/ethnicity, and currently taking a stable dose of metformin (1-2 g daily) will be recruited from the Spokane community to participate in this three-arm, open-label, fixed-sequence, crossover study. The progression of subject recruitment and study participation are provided (**Figure 1**).

PRE-SCREENING

Inclusion criteria:

- Men and women between the ages of 18 and 64
- Medically diagnosed with type 2 diabetes and currently taking a stable dose of metformin (1-2 g daily) but otherwise healthy
- HbA1c < 8% as determined by laboratory analysis on initial screening
- Not taking any medications (prescription and non-prescription) or dietary/herbal supplements known to alter the pharmacokinetics of midazolam, metformin, and/or goldenseal constituents
- Willing to abstain from consuming dietary/herbal supplements and citrus juices for several weeks prior to study
- Willing to abstain from consuming alcohol, caffeinated beverages, and/or other caffeine-containing products the evening before the first day of a study phase.
- Willing to use an acceptable method of contraception that does not include oral contraceptive pills or patches (such as abstinence, copper IUD, condom)
- Have the time to participate

Exclusion criteria:

- Any current major illness or chronic illness such as (but not limited to) type 1 diabetes, kidney disease, hepatic disease, hypertension, coronary artery disease, chronic obstructive pulmonary disease, cancer, or HIV/AIDS
- HbA1c ≥ 8% as determined by laboratory analysis from screening visit
- History of anemia or any other significant hematologic disorder
- History of drug or alcohol addiction or major psychiatric illness
- Women who are pregnant or nursing
- Have a history of intolerance or allergy to midazolam and/or goldenseal products
- Taking medications, both prescription and non-prescription (including dietary supplements/ herbal products) known to alter the pharmacokinetics of midazolam, metformin, and/or goldenseal constituents

SCREENING VISIT

Potential eligible subjects, based on the inclusion/exclusion criteria, will present for a screening visit at the Clinical Research Unit in the Nursing Building (SNRS 417) on the Spokane campus. The screening coordinator will consult with the participants and will address any questions or concerns. Informed consent and HIPAA authorization form will be obtained after full explanation of the study protocol. Consented subjects will undergo the following:

- A medical history and physical exam
- Complete blood count with differential, basic metabolic panel, liver function tests, and hemoglobin A1C
- Routine urine analysis
- Urine pregnancy test for female subjects of child-bearing potential (prior to enrollment in the study and prior to each phase of the study using in-home urinalysis pregnancy screens)

STUDY DESIGN

This clinical study will consist of three arms and will follow the fixed-sequence depicted (**Figures 2 and 3**). Arm 1 (control), Arm 2 (acute goldenseal exposure), and Arm 3 (chronic goldenseal exposure) will each consist of one 14-hour inpatient visit followed by 1 outpatient visit the subsequent day. Subjects will be administered the following in each arm:

Baseline (Arm 1)

During the inpatient visit, a subtherapeutic dose of the control drug midazolam (0.5 mg) will be administered intravenously *via* a pre-placed indwelling peripheral catheter by a registered nurse.

Acute goldenseal exposure (Arm 2)

During the inpatient visit, participants will be administered a single 3-gram dose of a well-characterized, oral goldenseal product in conjunction with the subtherapeutic, intravenous dose of midazolam.

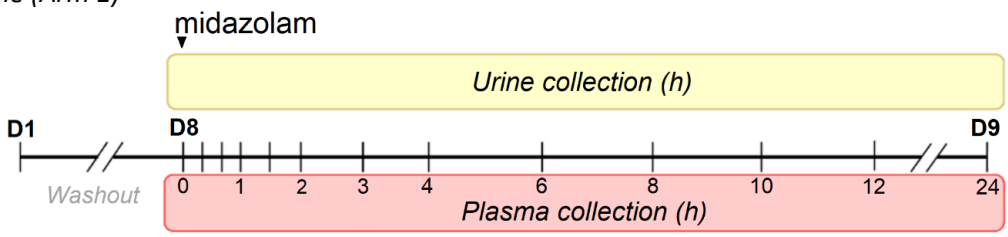
Chronic goldenseal exposure (Arm 3)

Participants will self-administer two capsules (1 g) of goldenseal by mouth 3 times daily (~4 hours apart) for 27 consecutive days. On the 28th day, participants will return to SNRS 417 for the inpatient visit. During the visit, they will be administered the same intravenous dose of midazolam as in Arms 1/2 and two capsules (1 g) of goldenseal; the goldenseal product will be administered two additional times throughout the inpatient visit (~4 hours apart).

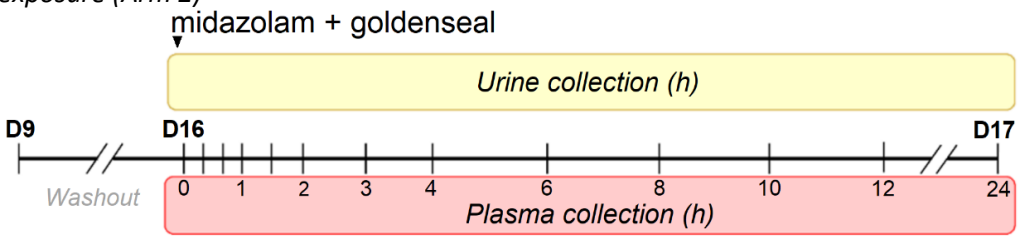
Figure 2. *Overview of study sequence.*

Figure 3. *Detailed timelines of the sequential arms.*

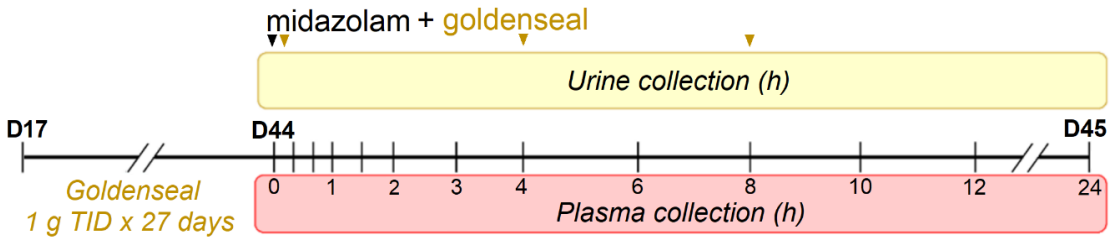
Baseline (Arm 1)



Acute exposure (Arm 2)



Chronic exposure (Arm 3)



Study days. Subjects will be asked to present to the Clinical Research Unit on the morning of each inpatient study day. Vital signs will be checked and recorded on case forms. Subjects will be asked about any change to their health status; responses will be recorded on case forms. A peripheral IV line will be placed in one arm, and a blood sample (11 mL) will be drawn through the IV line, after which subjects will receive midazolam (control) or midazolam and goldenseal (acute/chronic exposure) in conjunction with them taking their prescribed oral metformin dose. Blood (6 mL) will be drawn from the IV line 20 minutes, 40 minutes, 1 hour, 1.5 hours, and 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, and 12 hours post-midazolam administration. Urine will be collected into a jug from 0-12 and 12-24 hours. An additional blood sample (3 mL) will be collected during Arm 1 for genotyping of drug metabolizing enzymes or transporters that may affect the pharmacokinetics of midazolam, metformin, and/or goldenseal constituents. After the 12-hour blood draw, subjects will be allowed to leave the Clinical Research Unit once deemed safe by the study coordinator. Subjects will be allowed to take the 12-24 urine jug home and will return it the subsequent day. Subjects will be asked to return to the Clinical Research Unit the subsequent day for the outpatient blood draw (6 mL) *via* venipuncture at 24 hours post-midazolam administration. All arms of the study will involve an identical blood sampling and urine collection strategy.

Subjects will be asked to refrain from consuming any dietary/herbal supplements or citrus juices for at least 1 week prior to each inpatient visit and to refrain from alcohol and caffeinated beverages the evening before each inpatient day.

Goldenseal product acquisition. A well-characterized, unadulterated goldenseal product will be supplied by our longstanding natural products chemist collaborators at the University of North Carolina at Greensboro led by Drs. Nicholas Oberlies and Nadja Cech. They have acquired the product manufactured by Solaray®, which has been chemically characterized and tested for contaminants, including microbes, heavy metals, pesticides, residual solvents, and other adulterants. All of these contaminants were confirmed to be below the allowable limits, thus suitable for human consumption.

Midazolam acquisition. Dr. John White, a longstanding collaborator/co-investigator and registered pharmacist in WA, will oversee the acquisition and storage of the pharmaceutical-grade intravenous midazolam solution.

Pharmacokinetic and statistical analysis. The pharmacokinetics of midazolam, midazolam metabolites, metformin, and goldenseal constituents will be determined using industry standard Phoenix WinNonlin (v8.3m, Certara, Princeton, NJ). The primary endpoints will be the AUC and C_{max} of metformin, specifically the metformin/control ratio of log-transformed data, with a predefined no effect range of 0.80-1.25.[1] A two one-sided testing procedure, as recommended by the FDA Guidance for Industry,[1] will be used for the primary endpoint analysis. That is, if this ratio lies between 0.80 and 1.25, a goldenseal-midazolam interaction is not evident. A sample size of 20 evaluable subjects will provide 80% power to detect a 20% change in the primary endpoint with a Type I error of 0.05, assuming a 25% intra-individual variability in metformin AUC and C_{max}. Secondary endpoints (*e.g.*, exposure/control ratio of $t_{1/2}$, t_{max}, and oral clearance for metformin and exposure/control ratio of AUC, C_{max}, $t_{1/2}$, t_{max}, and oral clearance for midazolam, midazolam metabolites, and goldenseal constituents) will be evaluated using a paired Student's *t*-test or Wilcoxon signed-rank test as appropriate; a p-value <0.05 will be considered statistically significant.

ROLES OF STUDY PERSONNEL

Mary Paine, RPh, PhD

Principal investigator

Oversee all aspects of the study

Deena Hadi, BS

Program manager

Coordinate study days with staff and subjects

Manage finances and study supply logistics

Matt Layton, MD, PhD
- Physician of record/ co-investigator
- Obtain medical history and perform physical exam
- On-call physician for the duration of clinical activities

John White, PA-C, PharmD
- Authorized licensed designee of Dr. Layton/ co-investigator
- Obtain medical history and perform physical exam
- Acquire study drugs

James Nguyen, PharmD
- Study coordinator/ co-investigator
- Conduct screening and clinical activities
- Assist in all aspects of the study

Sabrina Judson
- Study coordinator
- Conduct screening and clinical activities
- Process and analyze biofluids

Rakshit Tanna
- Study assistant
- Process and analyze biofluids

Kennedy Erickson
- Study assistant
- Process and analyze biofluids

REFERENCES

1. Food and Drug Administration Center for Drug Evaluation and Research (2017): Clinical Drug Interaction Studies—Study Design, Data Analysis, and Clinical Implications Guidance for Industry (draft guidance).