NCT #04392011

Assessing the pharmacokinetics and drug interaction liability of kratom, an opioid-like natural product

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8/12/2019

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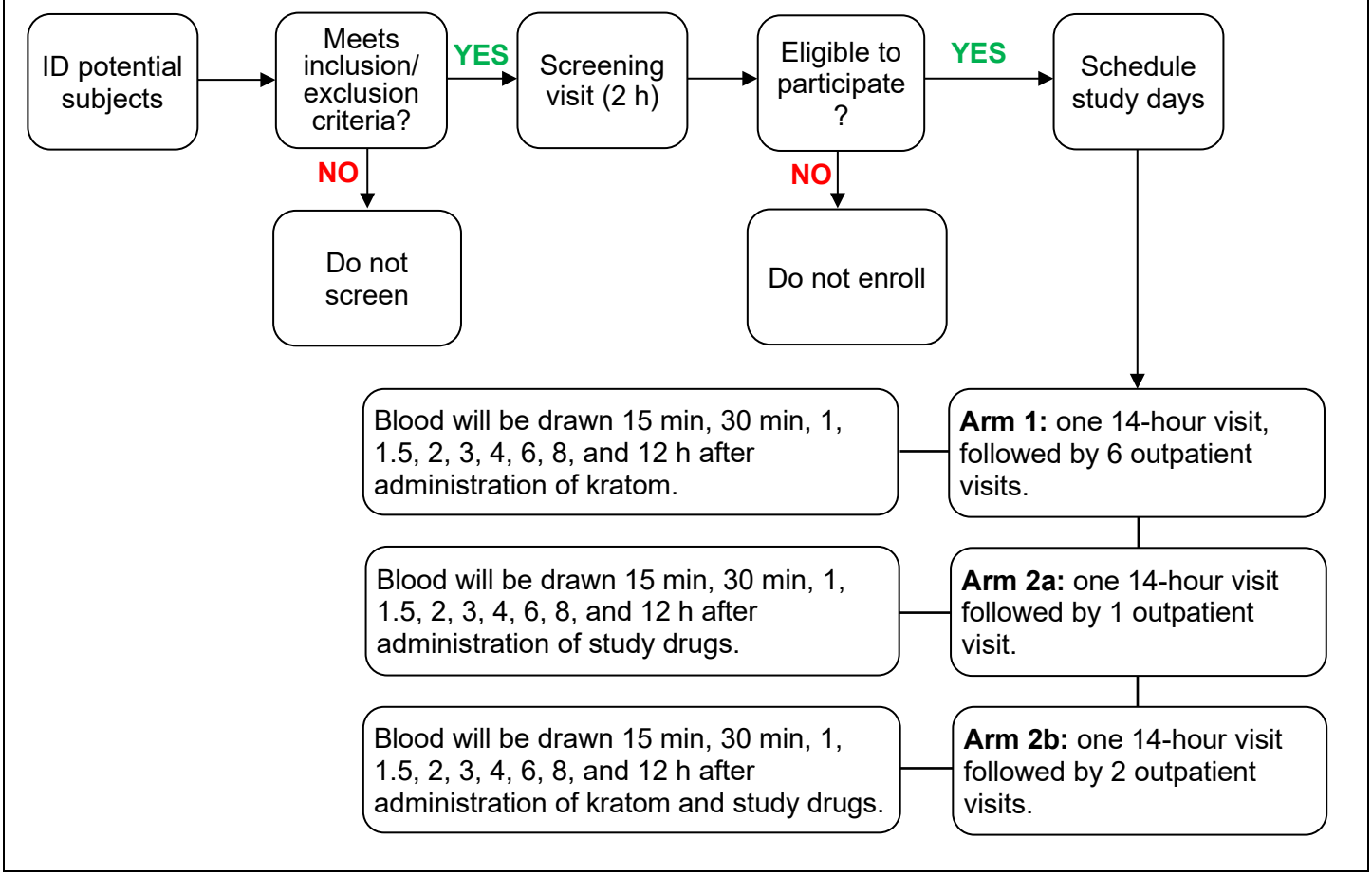
FIGURE 1. *Overview of procedures.*



SUBJECTS

Healthy adult volunteers who are intermittent users of kratom ('non-naïve') will be recruited from the local community to participate in this safety study (***FIGURE 1***). Intermittent users are defined as those who use from 2-8 grams of kratom at least once per month but no more than three times per day within the past six months prior to screening and are not trying to quit.

PRE-SCREENING

Inclusion criteria:

- Men and women, aged from 18-55 years and healthy
- Not taking any medications (prescription and non-prescription) or dietary/herbal supplements known to alter the pharmacokinetics of either study drug or kratom constituents
- Willing to abstain from consuming dietary/herbal supplements and citrus juices for several weeks
- Willing to abstain from consuming caffeinated beverages or other caffeine-containing products the evening before and morning of the first day of a study arm
- Willing to abstain from consuming any alcoholic beverages for one day prior to any study day, during the 14-hour inpatient days, and for the 5 and/or 1 outpatient visit(s) following 14-hour visit
- 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
- Are non-naïve kratom users (intermittent users who are not trying to quit), *i.e.* an intermittent user who uses between 2 to 8 grams of kratom at least once per month but no more than three times per day within the past six months prior to screening.

- Carry a *CYP2D6* genotype designated as having an intermediate, extensive, or ultra-extensive metabolizer phenotype
- Written informed consent (and assent when applicable) obtained from subject or subject's legal representative and ability for the subject to comply with the requirements of the study
- History of self-reported kratom use (self-reported intake ≥1 time per month)

Exclusion criteria:

- Men and women under the age of 18 or over the age of 55
- Any current major illness or chronic illness such as (but not limited to) kidney disease, hepatic disease, diabetes mellitus, hypertension, coronary artery disease, chronic obstructive pulmonary disease, cancer, or HIV/AIDS
- No previous exposure to kratom
- History of anemia or any other significant hematologic disorder
- History of drug or alcohol addiction or major psychiatric illness
- A need for chronic opioid analgesics
- Use of opioid analgesics 3 weeks prior to initiation of the study
- An imminent likely need for opioid analgesics (*e.g.*, planned dental or surgical procedure)
- Female and pregnant or nursing
- Have a history of allergy to kratom or other opioid-containing natural products, other opioids, midazolam or other benzodiazepines, or dextromethorphan.
- Taking concomitant medications, both prescription and non-prescription (including dietary supplements/herbal products), known to alter the pharmacokinetics of either study drug or kratom constituents
- Carry a *CYP2D6* genotype designated as having a poor metabolizer phenotype
- Presence of a condition or abnormality that, in the opinion of the Investigator, would compromise the safety of the patient or the quality of the data
- History of sleep apnea
- Use of monoamine oxidase inhibitors (MAOIs) 14 days prior to the initiation of the study
- A need for chronic opioid analgesics
- Recreational drug use other than kratom, such as amphetamines, benzodiazepines, cocaine, marijuana, MDMA, opioids, and PCP
- Current recreational use of marijuana
- History of intolerance to kratom
- Out-of-range clinical laboratory value that the study physician considers participation in the study a health risk
- Subjects with seizure disorders

SCREENING VISIT

Potential eligible subjects, based on the inclusion/exclusion criteria, will present for a screening visit at the Nursing Building or Sleep and Performance Research Center on the Spokane campus. Informed consent will be obtained after full explanation of the study protocol. Consented subjects will undergo the following:

- A medical history and physical exam
- CBC with differential, electrolytes, liver function tests, serum creatinine
- Routine urine analysis
- Urine toxicology screen for multiple common drugs of abuse, including several opioids
- 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)
- Genotyping for common *CYP2D6* single nucleotide polymorphisms to determine CYP2D6 metabolizer status (*i.e.*, poor or extensive metabolizers)

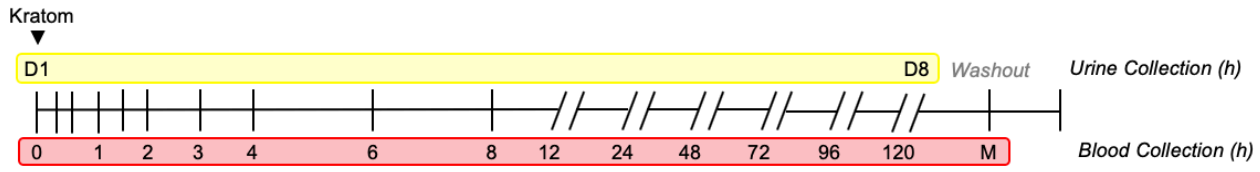
STUDY DESIGN

FIGURE 2. *Overview of study design.*

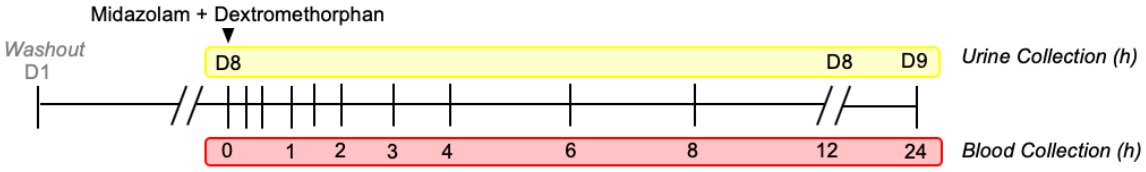
Screening	≥1 week washout	Arm 1	≥1 week washout	Arm 2a	≥1 week washout	Arm 2b

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

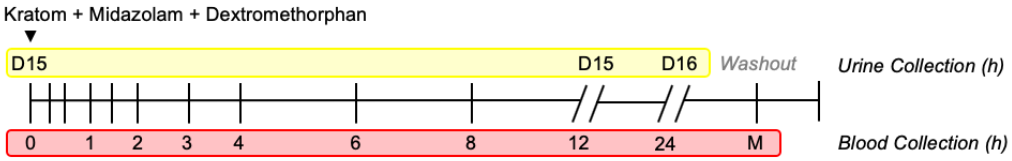
3.1. *Arm 1*



3.2. *Arm 2a*



3.3. *Arm 2b*



M = Midpoint blood collection during kratom washout period to adequately characterize kratom constituent half-life

This study will consist of two study arms (***FIGURES 2 and 3***). Arm 1 will include one 14-hour inpatient visit, followed by 6 outpatient visits. Arms 2a and 2b will include one 14-hour inpatient visit each; Arm 2b will include one additional outpatient visit. If a subject elects to participate in Arm 2, he/she will undergo a washout period of at least 7 days after completing Arm 1. A washout period of at least 7 days will separate Arms 2a and 2b. Subjects will be administered the following:

Arm 1: Kratom (2 g) by mouth as a tea.

Arm 2a: Two liquid-filled capsules of dextromethorphan (15 mg each, 30 mg total) by mouth + midazolam syrup (2.5 mg) by mouth.

Arm 2b: Kratom (2 g) by mouth (as a tea) + two liquid-filled capsules of dextromethorphan (30 mg) by mouth + midazolam (2.5 mg) syrup by mouth.

Study days. Subjects will be asked to present to the Clinical Research Unit in the Nursing Building or the Sleep and Performance Research Center on the morning of each 14-hour inpatient visit. Vital signs will be checked and recorded on case forms. Subjects will be asked of any change to their health status; responses will be recorded on case forms. An intravenous line will be placed in one arm, and two blood samples (5 mL and 3 mL) will be drawn through the intravenous line, after which subjects will receive kratom tea alone (Arm 1) and/or drug cocktail alone (Arm 2a) and drug cocktail + kratom tea (Arm 2b). Blood will be drawn from the intravenous line 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post-kratom tea and/or post-drug cocktail administration. Urine will be collected into multiple jugs from 0-120 hours (Arm 1) and/or from 0-24 hours (Arms 2a and 2b). 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 asked to return to the Clinical Research Unit for outpatient blood draws (5 mL) via venipuncture at 24, 48, 72, 96, and 120 hours post-kratom administration during Arm 1 and 24-hours post kratom and/or study drug administration. Subjects will be asked to return to the Clinical Research Unit for one additional outpatient blood draw (5 mL) via venipuncture up to 7 days after the 120-hour blood draw during Arm 1 and after the 24-hour blood draw during Arm 2b.

Each of the two study arms will be separated by at least 7 days, as the half-life of mitragynine is ~24 hours. Subjects will be asked to refrain from consuming any dietary/herbal supplements or citrus juices for at least 1 week prior to each 14-hour inpatient visit and for the duration of the study and to refrain from alcoholic and caffeinated beverages the evening before and the morning of each inpatient and outpatient visit.

Kratom product acquisition. A well-characterized, standardized, unadulterated, contaminant-free kratom product will be obtained from longstanding natural products chemist collaborators at the University of North Carolina at Greensboro led by Dr. Nicholas Oberlies.[1] The Oberlies group has selected and tested Moon Kratom Yellow Indonesian, lot 51, as the kratom product to be administered. The Oberlies group has provided the Paine group with natural product study materials suitable for human consumption for more than 10 years.

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

Pharmacokinetic and statistical analysis. Blood and urine samples for analysis of midazolam, midazolam metabolites, dextromethorphan, dextromethorphan metabolites, and kratom constituent concentrations will be collected. The pharmacokinetics of midazolam, midazolam metabolites, dextromethorphan, dextromethorphan metabolites, and kratom constituents will be determined using traditional noncompartmental analysis methods and the pharmacokinetics analysis software, Phoenix WinNonlin (v7.0, Certara, Princeton, NJ). A two one-sided testing procedure will be used for the primary endpoint analysis as recommended by the FDA for drug-drug interactions studies.[2] Specifically, if the treatment/baseline ratio of log-transformed midazolam AUC lay between the predefined no-effect range (0.75-1.33), a kratom-midazolam interaction will not be evident. Secondary endpoints (*e.g.*, treatment/baseline ratio of C_{max}, $t_{1/2}$, t_{max}, and oral clearance for midazolam and treatment/baseline ratio of AUC, C_{max}, $t_{1/2}$, t_{max}, and oral clearance for midazolam metabolites, dextromethorphan, and dextromethorphan metabolites) 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. For study Arm 1, 6 evaluable subjects, who may or may not elect to participate in Arm 2, are deemed sufficient for definitive characterization of the half-life of the kratom constituents. For study Arm 2, a sample size of 12 evaluable subjects will provide 80% power to detect a 25% change in the primary endpoint (midazolam AUC) with a Type I error of 0.05, assuming 20% intra-individual variability in midazolam AUC.

ROLES OF STUDY PERSONNEL

Mary Paine, RPh, PhD
- Principal investigator
- Oversee all aspects of the study

Matthew Layton, MD, PhD
- Study physician
- Obtain medical history and perform physical exam
- Be on-call for the entire study period in case of adverse events

John White, PA-C, PharmD
- Authorized licensed designee of Dr. Layton
- Acquire study drugs

Deena Hadi, BS
- Schedule study days with staff and subjects
- Oversee financial matters
- Order study supplies

James Nguyen, PharmD Candidate
- Co-study coordinator
- Assist in all aspects of the study

Sabrina Judson, PharmD Candidate
- Co-study coordinator
- Assist in all aspects of the study

Rakshit Tanna, PhD student
Co-study coordinator
Assist in all aspects of the study

Karen Vo, PharmD Candidate
Assist in all aspects of the study

Dallas Carbaugh, PharmD Candidate
Assist in all aspects of the study

Emily Gallagher, PharmD Candidate
Assist in all aspects of the study

REFERENCES

1. Kellogg JJ, Paine MF, McCune JS, Oberlies NH, and Cech NB. Selection and characterization of botanical natural products for research studies: a NaPDI Center recommended approach. *Nat Prod Rep*. 2019 Jan 25. doi: 10.1039/c8np00065d. [Epub ahead of print]
2. U.S. Food and Drug Administration. Drug Interactions: Relevant Regulatory Guidance and Policy Documents: https://www.fda.gov/drugs/drug-interactions-labeling/drug-interactions-relevant-regulatory-guidance-and-policy-documents (accessed August 11, 2019).