ABSOLUTE BIOAVAILABILITY/PHARMACOKINETIC AND RESIDUAL DRUG ANALYSIS OF THE TRANSDERM SCŌP® SYSTEM IN HEALTHY ADULTS

Short title: Scopolamine Release from Transdermal Patches in Healthy Adults

Principal Investigator:

Nicole K. Brogden (contact), PharmD, PhD

Medically Accountable Investigator:

Ken-ichi Ueda, MD

Principal investigator contact:
Nicole K. Brogden, PharmD, PhD
Assistant Professor, Department of Pharmaceutical Sciences and Experimental Therapeutics
University of Iowa College of Pharmacy
115 S. Grand Ave, S421
Iowa City, IA 52242
Phone: 319-335-8752
Fax: 319-335-9349
Email: nicole-brogden@uiowa.edu

09 December 2016

Study title:	Absolute Bioavailability/Pharmacokinetic and Residual Drug Analysis of the Transderm Scōp® System in Healthy Adults
Principal Investigator	Nicole K. Brogden, PharmD, PhD
Population:	Healthy, non-smoking adults age 18-65 years
Number of Sites:	Single site: University of Iowa College of Pharmacy/ University of Iowa Clinical Research Unit
Study Duration:	Approximately up to 12 months
Subject Participation Duration:	Approximately 5 – 7 weeks, including the screening period

Description of Study Design
This will be a two arm, open-label, crossover, two treatment sessions study (n=24 healthy adult subjects) with one week washout period between each study session. The two study sessions include an intravenous administration of scopolamine hydrobromide and a transdermal administration of a single strength of the reference listed drug (RLD) Transderm Scōp® patch. Each subject will be his/her own control.

Study products
- Transderm Scōp® patch containing scopolamine (1.5 mg) to be worn for 3 days (72 hr)
- Single intravenous (0.4 mg) administration of scopolamine hydrobromide (0.4 mg/mL)

Study enrollment
Only adult subjects who meet the inclusion/exclusion criteria will be eligible for enrollment into the study. Twenty-four subjects will be recruited, and ten alternates who could replace subjects who drop out from the study for any unforeseen reason. The study population selected for this study includes healthy adult men and women ages 18 to 65, inclusive. Enrollment will continue until 24 complete the study. The selection criteria are designed to exclude persons who might have medical conditions that could pose a safety risk and persons whose medical conditions might interfere with objectives and results of the study.

Inclusion Criteria
Subjects are eligible for this study if they fulfill the inclusion criteria specified below:

1. Men or non-pregnant women of any ethnic background between the age of 18 and 65 years old.
2. Subjects must be non-smokers (must have refrained from the use of nicotine-containing substances, including tobacco products (e.g., cigarettes, cigars, chewing tobacco, gum, patch or electronic cigarettes) over the previous 12 months and are not currently using tobacco products.
3. Provide written informed consent before initiation of any study procedures.
4. Available for follow-up for the planned duration of the study.
5. Able to communicate well with the investigators.
6. Able to adhere to the study protocol schedule, study restrictions and examination schedule.
7. Subjects who are within their ideal body weight (BMI between 18-29.9 kg/m^2).
8. Demonstrate comprehension of the protocol procedures and knowledge of study, as demonstrated a study member filling out a consent checklist form to verify that the subject understands all aspects of the study including the purpose, procedures, risks and benefits.

9. Subjects deemed to be healthy as judged by the Medically Accountable Investigator (MAI) and determined by medical history, physical examination, and medication history.
10. Negative urine drug screening test.
11. Have a normal blood pressure (systolic: 90-140 mmHg; diastolic: 50-90 mmHg) and heart rate (55-100 bpm).
12. Have normal screening laboratories for WBC, Hgb, Hct, platelets, sodium, potassium, chloride, bicarbonate, BUN, creatinine, ALT, AST, and total bilirubin.
13. Have normal screening laboratories for urine protein and urine glucose.
14. Female subjects must be of non-childbearing potential (defined as surgically sterile [i.e. history of hysterectomy or tubal ligation] or postmenopausal for more than 1 year [no bleeding for 12 consecutive months]), or if of childbearing potential must be non-pregnant at the time of enrollment and on the morning of the first day of each study treatment session, and must agree to use hormonal or barrier birth control such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence, or a vasectomized partner.
15. Agrees not to participate in another clinical study during the study period unless the study is in the follow up phase and it has been 1 month since the subject received any experimental agents or treatments. The subject also agrees not to participate in an investigational drug study for at least 1 month after last procedure day.
16. Agrees not to donate blood to a blood bank throughout participation in the study and for at least 2 months after last procedure day.
17. Have a normal ECG; must not have the following to be acceptable: pathologic Q wave abnormalities, significant ST–T wave changes, left ventricular hypertrophy, right bundle branch block, left bundle branch block (sinus rhythm is between 55–100 beats per minute).

Exclusion Criteria

Subjects will be excluded for any of the following conditions/reasons:

1. Women who are pregnant or lactating or have a positive serum pregnancy test at enrollment or positive urine pregnancy test on the morning of the first day of any procedure session.
2. Smokers (current use or use over the previous 12 months of nicotine-containing substances, including tobacco products (e.g., cigarettes, cigars, chewing tobacco, gum, patch or electronic cigarettes)).
3. Participation in any ongoing investigational drug trial or clinical drug trial period unless the study is in the follow up phase and it has been ≥ 1 month since the subject received any experimental agents or treatments..
4. Abnormal vital signs, defined as:
    - Hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg) at rest on 2 separate days.
    - Heart rate <55 at rest on 2 separate days
    - Respiratory rate ≤ 11 to ≥ 18 breaths per minute
5. Temperature >38.0ºC (100.4ºF) or symptoms of an acute self-limited illness such as an upper respiratory infection or gastroenteritis within 7 days of application of the scopolamine TDDS.
6. History of chronic obstructive pulmonary disease.
7. Positive urine drug screening test.
8. Use of any prescription medication during the period 0 to 30 days or over-the counter medication during the period 0 to 3 days before entry to the study (vitamins, herbal supplements and birth control medications not included).
9. Use of medications or treatments that would significantly influence or exaggerate responses to the test product or that would alter inflammatory or immune response to the product (e.g. antihistamines [within 72 hours prior to dosing], systemic or topical corticosteroids [within 3 weeks prior to dosing], cyclosporine, tacrolimus, cytotoxic drugs, immune globulin, Bacillus Calmette-Guerin [BCG], monoclonal antibodies, radiation therapy).

10. Donation or loss of greater than one pint of blood within 60 days of entry to the study.
11. Any prior serious adverse reaction or hypersensitivity to scopolamine, or any of the inactive ingredients in the patch (light mineral oil, polyisobutylene, polypropylene and aluminized polyester film).
12. Have a diagnosis of schizophrenia or other major psychiatric diagnosis.
13. Received an experimental agent (vaccine, drug, biologic, device, blood product or medication) within 1 month before enrollment in this study or expects to receive an experimental agent during the study.
14. Medical history of a serious chronic condition, including (but not limited to): allergic conditions such as anaphylaxis, asthma or generalized drug reactions; any seizure disorder; glaucoma (open or closed angle); history of pyloric or urinary bladder neck obstruction; intestinal obstruction; difficulty swallowing; stomach or bowel problems (e.g, blockage, muscle weakness, ulcerative colitis, Crohn's disease); bleeding disorders; acid reflux disease; myasthenia gravis; allergy to belladonna alkaloids; impaired hepatic or renal function.
15. Any condition that would, in the opinion of the MAI, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol.
16. Inability to communicate or co-operate with the investigators.
17. Medical history of significant dermatologic diseases or conditions, such as atopy, psoriasis, vitiligo or conditions known to alter skin appearance or physiologic response (e.g. diabetes, porphyria).
18. History of significant dermatologic cancers (e.g. melanoma, squamous cell carcinoma), except basal cell carcinomas that were superficial and did not involve the investigative site.
19. History of consumption of alcohol within 24 hours prior to dose administration.
20. Subject has an obvious difference in skin color between arms or the presence of a skin condition, excessive hair at the application site, sunburn, raised moles and scars, open sores at application site, scar tissue, tattoo, or coloration that would interfere with placement of test articles, skin assessment, or reactions to drug.
21. Use of monoamine oxidase inhibitors 21 days prior to study.
22. Within 4 weeks prior to dosing, use of medications or treatments that would significantly influence or exaggerate responses to the test product or that would alter inflammatory or immune response to the product or agents deemed to be immunosuppressive as determined by physician investigator.
23. Planned MRI scan of the head during TDDS wear.

Study schedule

For the treatments, either the patch will be applied behind the ear or the drug will be intravenously administered. Blood samples will be obtained as follows (based on administration route):

- 60 min pre-application and then up to 120 hr (5 days), during 3 day wear and 2 day post patch removal
- 60 min pre-IV administration and then up to 48 hr (2 days) post start of IV administration

Residual drug analysis determination of strength

In conjunction with the above described study, residual drug analysis will also be conducted for the worn patches. All items coming into contact with the patch during application and removal from the subject and storage for analytical retention are analyzed for drug content.

- After application of the patch to the subject, the pouch, release liner and all items coming into contact with the patch are retained for analysis.
- The worn patch is retained for drug content analysis.
- Upon removal of the product after prescribed wear period, the skin (at site of application) is swabbed and the swab is retained for drug content analysis.

Study Objectives
The objectives of these studies are: 1) to determine the absolute bioavailability of scopolamine patch, 2) to determine the residual drug content in worn patches, and 3) determine absorption rates from patches based on residual drug content and derived PK parameters.

Study Outcome Measures
The outcomes of this study ae to determine pharmacokinetic parameters of scopolamine in healthy adult subjects. The primary outcome measure of the study is to determine the maximum serum concentration of scopolamine (C_{max}). The secondary outcome measures include clearance (Cl), volume of distribution (V), elimination rate constant (K_{el}), time of maximum serum concentration (T_{max}) of scopolamine, and area under the serum concentration-time curve (AUC). In addition, we will determine residual drug content from worn Transderm Scōp® patches to estimate total amount of absorbed scopolamine.

Pharmacokinetic and statistical considerations
Pharmacokinetics (PK) Analyses
Scopolamine concentrations will be measured in serum samples collected from each subject. Actual sampling times will be used to estimate PK parameters. Non compartmental and compartmental analyses will be conducted to estimate the primary PK parameters such as clearance (Cl), volume of distribution (V), elimination rate constant (K_{el}), maximum serum concentration (C_{max}); time of maximum serum concentration (T_{max}) and area under the serum concentration-time curve (AUC). Absolute bioavailability will be calculated as follows:

$$Absolute\ bioavilability = \frac{AUC_{patch}/Dose_{patch}}{AUC_{IV}/Dose_{IV}}$$

Equation 1: For determination of the absolute bioavailability for the Transderm Scōp® patch. The patch refers to the Transderm Scōp® transdermal system.

Statistical Analysis Plan
Descriptive statistics for drug content (i.e., arithmetic mean, median, standard deviation, minimum amount, maximum amount, coefficient of variation) will be calculated. In addition, mass balance will be calculated. Drug content in the unworn patch will be analyzed, the mean amount will be calculated and will be used to estimate amount of drug absorbed after wearing the transdermal system. Unworn systems will all be from the same lot (as printed on the patch pouch), and a minimum of 10 unworn systems will be analyzed for drug content. Drug absorption will be determined by subtracting the residual drug content from the initial drug amount as mentioned on the product label.