Determination of Serum Oxybutynin Levels after Using Oxybutynin Transdermal Delivery System and Transdermal Gel with and without Standardized Heat Application in Healthy Human Volunteers

Short title: Effect of Heat on Oxybutynin Release and Absorption from Oxybutynin Products

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STATEMENT OF COMPLIANCE

This trial will be conducted in compliance with the protocol, International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP) and the applicable Food and Drug Administration and other Department of Health and Human Services regulatory requirements.

All key personnel (all individuals responsible for the design and conduct of this study) have completed Human Subjects Protection Training.

PROTOCOL SUMMARY

Title:	Determination of Serum Oxybutynin Levels after Using Transdermal Oxybutynin Patch and Gel with and without Standardized Heat Application in Healthy Human Volunteers
Population:	Healthy adults age 18 - 45 years
Number of Sites:	Single site: University of Maryland School of Medicine
Study Duration:	Approximately up to 1 year
Subject Participation Duration:	Approximately 12 weeks including the screening period
Description of Study Product:	Oxybutynin (Oxytrol® for Women, 36 mg patch), Actavis Pharma, Inc.; Oxybutynin (Gelnique®) 10% gel, Watson Pharmaceuticals, Inc
Objective:	The aim of the present study is to generate human pharmacokinetic (PK) data in healthy subjects for the purpose of establishing a reference for in vitro-in vivo correlation (IVIVC) with an in vitro model following the application of oxybutynin products: Oxytrol® for Women (oxybutynin patch) with and without heat application and Gelnique® (oxybutynin 10% gel)with and without occlusion.
Description of Study Design:	The study will be an open-label, crossover study (n=12 healthy subjects) over 12 weeks includes four study sessions with up to a 45 day screening period with one week washout period between study sessions. The study contains four study sessions: • **Study Session 1:** Oxytrol® for Women patch containing 36 mg each of oxybutynin to be worn for 30 h. • **Study Session 2:** Gelnique® gel containing 10% oxybutynin (0.5 g of gel/200 cm^2/upper arm) to be applied (and not wiped) for 12 h without occlusion. • **Study Session 3:** Oxytrol® for Women patch containing 36 mg each of oxybutynin to be worn for 30 h. The heating pad will be set to induce a skin temperature of 42.0 ± 4°C and applied for 1 hour 30 minutes at 24 h and at 30 h after application of the Oxytrol® for Women patch. Patch to be

worn for 30 h.

- **Study Session 4:** Gelnique® gel containing 10% oxybutynin (0.5 g of gel/200 cm^2/upper arm) to be worn for 12 h with occlusion from 7 through 10 h.

A) Pharmacokinetics (PK)

Each subject will be his/her own control (pre-dose blood sample) and each subject will sign an institutional review board–approved consent form explaining the purpose, nature, risks, benefits, and duration of the study. The study will be conducted in accordance with good clinical practice guidelines and with the ethical principles originating in the Declaration of Helsinki.

The subject's skin in the area of application (upper arm) will be relatively free of hair before patch/gel application. Blood samples (approximately 4 mL each) will be drawn in BD vacutainer tubes. Blood samples will be obtained as follows:

- Within 60 min pre-application and then up to 34 h 30 min after patch application. Within 60 min pre-application and then up to 12 h after gel application.

B) Residual Drug Analysis of Oxytrol® for Women Patch

In conjunction with the above described study, residual drug analysis will also be conducted for the previously worn Oxytrol® for Women patches from Study Session 1 and 3.

- Prior to administration to the subject as described in Part A, patches will be weighed and the weight recorded.

- The pouch, release liner and all items coming into contact with the patch (gloves, forceps, etc..) applied in Part A will be retained for analysis.

- The used patch will be retained for drug content analysis.

- All items coming into contact with the patch during removal from the subject will be stored in a separate labeled sealable foil pouch until analyzed for drug content.

1 KEY ROLES

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

There are numerous transdermal delivery systems (TDS) that are currently available in the United States, the first of which was approved by the Food and Drug Administration (FDA) in 1979 [1]. TDS are very attractive, convenient and easy to use systems and are available in various forms including patches (matrix or reservoir), sprays, gels, and ointments. Drug release from these TDS varies significantly and is dependent on a number of factors including system design, physicochemical properties of the drug, excipients, occlusion, sweat, skin condition, skin type and temperature. Investigating the influence of these factors on drug release from reference products that are often available in different forms is important to ensure that one formulation is not less safe than other formulations. In this proposal we will focus on investigating the influence of heat and occlusion on drug release from oxybutynin products (patch and gel). Systemic absorption of drugs is dependent on cutaneous blood flow. Application of, or exposure to heat, allows gradual increase in cutaneous blood flow and an increase in the absorption rate and hence can increase drug permeation from TDS. Indeed, exposure to heat has been demonstrated to increase drug release from patches, which led to increased serum concentrations of numerous drugs (e.g., fentanyl and nicotine) and raised a number of safety concerns [2-7]. As a result, almost all patches that are currently available have warnings against heat exposure. Occlusion effect on semi-solid formulations has not been widely investigated. Skin occlusion prevents water loss from skin surface thus increasing hydration of stratum corneum. Increased stratum corneum hydrophilicity can alter the movement of drug molecules through skin resulting in increased drug permeation [15].

2.2 Rationale

The goal of this study is to conduct in vivo studies to compare the influence of heat and occlusion on oxybutynin drug release from FDA approved products; Oxytrol® for Women patch versus Gelnique® gel. While there is data in the literature for heat and occlusion effect on different active pharmaceutical ingredients (APIs), specifically RLD products, from exposure to external heating sources (heating pads, sauna, hot showers, exercising) and occlusion, there is a lack of data to demonstrate in vivo-in vitro correlation under heat exposure and occlusion. Therefore, to help ensure that gels and TDS are safe for patients, an in vitro setup is being developed to characterize the heat and occlusion effect for these TDS and gel systems, respectively, by correlating the in vivo data with in vitro data using the IVPT model with excised human skin. This necessitates that a small number of human subject heat effect and occlusion studies are performed

under controlled and monitored conditions with selected products, to serve as an in vivo reference for parallel IVPT heat effect and occlusion studies. The oxybutynin heat and occlusion effect studies described in this protocol are the final set in this series of studies. The intent of this research is to establish an IVIVC for the IVPT model in the specific context of heat and occlusion effect studies, so that IVPT studies can be utilized to evaluate these effects so future generic products are similar in quality to the brand name. In addition, the residual drug content of the used Oxytrol® for Women patches will be analyzed for the purpose of estimating the amount of drug absorbed.

Oxybutynin Products

	Oxytrol® for Women	**Gelnique® 10%**
Inactive ingredients	acrylic adhesive, polyester/ethylene-vinyl acetate film; siliconized polyester film and triacetin	alcohol USP, glycerin USP, hydroxypropyl cellulose NF, sodium hydroxide NF and purified water USP
Product	Patch	Gel
Manufacturer	Actavis Pharma, Inc.	Watson Pharmaceuticals, Inc.

3 OBJECTIVES

3.1 Study Objectives

The present study aims to:

1) Generate human PK data for the purpose of establishing an IVIVC model by collecting data following the application of oxybutynin products: Oxytrol® for Women (oxybutynin patch) and Gelnique® (oxybutynin 10% gel).

2) Determine serum oxybutynin concentrations after using Oxytrol® for Women (matrix type patch, Actavis Pharma, Inc.) with and without standardized heat application in healthy adult subjects and Gelnique® (gel, Watson Pharmaceuticals, Inc.) with and without occlusive backing application in healthy adult subjects..

3) Determine residual drug content of Oxytrol® for Women patch for the purpose of estimating amount of drug absorbed.

3.2 Study Outcome Measures

For the PK study the main outcome measure is the maximum serum concentration (C_{max}); time of maximum serum concentration (T_{max}) of oxybutynin and area under the curve (AUC) attained with and without heating for Oxytrol® for Women patch and with and without occlusive backing for Gelnique® gel. In addition, we will determine residual drug content from worn Oxytrol® for Women patch to estimate total amount of absorbed oxybutynin.

4 STUDY ENROLLMENT AND WITHDRAWAL

4.1 Subject Inclusion Criteria

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

1. Men or non-pregnant, non-lactating women who are of any ethnic background between the age of 18 and 45 years old.

2. Subjects must be non-smokers/tobacco users (must have refrained from the use of nicotine-containing substances, including tobacco products (e.g., cigarettes, cigars, chewing tobacco, snuff, gum, patches or electronic cigarettes) over the previous two months and are not currently using tobacco products.

3. Provide written informed consent before initiation of any of the study procedures.

4. Agree not to participate in another clinical trial/study or to participate in an investigational drug study for at least one month after the last study session.

5. Able to adhere to the study restrictions and protocol schedule.

6. Able to participate in all study sessions.

7. Subjects have upper arms large enough to allow for application of 200 cm^2 [31 in^2] area of gel. The arm distance from the greater tubercle to the olecranon process should be a minimum of 30 cm. The circumference of the upper arms should be a minimum of 30 cm.

8. Subjects deemed to be healthy as judged by the MAI and determined by medical history, physical examination and medication history.

9. Negative urine drug screening test (cannabinoids, amphetamines, barbiturates, benzodiazepine, cocaine, methadone, opiates, PCP).

10. Have normal screening laboratories for white blood cells (WBC), hemoglobin (Hgb), platelets, sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, alanine transaminase (ALT) and aspartate aminotransferase (AST).

11. Have normal screening laboratories for urine protein and urine glucose.

12. Female subjects must be of non-childbearing potential (as defined as surgically sterile [i.e., history of hysterectomy or tubal ligation] or postmenopausal for more than 1 year), or if of childbearing potential must be non-pregnant at the time of

enrollment and on the morning of each procedure day, 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.

13. Agree not to donate blood to a blood bank throughout participation in the study and for at least three months after the last procedure day.
14. 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).
15. Have normal vital signs:
    - Temperature 35-37.9°C (95-100.3°F)
    - Systolic blood pressure 90-165 mmHg
    - Diastolic blood pressure 60-100 mmHg
    - Heart rate 55-100 beats per minute
    - Respiration rate 12-20 breaths per minute

4.2 Subject Exclusion Criteria

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

1. Women who are pregnant, lactating, breast feeding or have a positive serum pregnancy test at enrollment or positive urine pregnancy test on the morning of any study session.
2. Smokers/tobacco users (current use or use over the previous two months of nicotine-containing substances, including tobacco products (e.g., cigarettes, cigars, chewing tobacco, snuff, gum, patch or electronic cigarettes).
3. Participation in any ongoing investigational drug trial/study or clinical drug trial/study.
4. History of chronic obstructive pulmonary disease or cor pulmonale, or substantially decreased respiratory reserve, hypoxia, hypercapnia or pre-existing respiratory depression.
5. Active positive Hepatitis B, C and/or HIV serologies (see *Appendix B*).
6. Positive urine drug screening test.
7. Use of chronic prescription medications during the period 0 to 30 days; or over-the-counter medications (e.g. bisphosphonates [to treat osteoporosis], anticholinergics [used to treat diseases like asthma, incontinence,

gastrointestinal cramps, and muscular spasms], antihistamines, topical corticosteroids) and short term (<30 days) prescription medications during the period 0-3 days before a study session [vitamin, herbal supplements and birth control medications not included)].

8. Donation or loss of greater than one pint of blood within 60 days of entry to the study.

9. Any prior allergies to oxybutynin, other ingredients in the patch or gel tested, to medical tape products or other skin patches.

10. Subject has problems with urinary retention, gastric retention or gastrointestinal obstruction.

11. Subject has ulcerative colitis.

12. Subject has gastric reflux disease or esophagitis.

13. Subject has uncontrolled narrow-angle glaucoma.

14. Subject has myasthenia gravis.

15. Received an experimental agent (vaccine, drug, biologic, device, blood product or medication) within one month before enrollment in this study or expects to receive an experimental agent during the study.

16. Any condition that would, in the opinion of the Medically Accountable Investigator (MAI), place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol.

17. Consumption (food or drink) of alcohol within 24 h prior to dose administration.

18. History as either reported by the subject or evident to the investigator of infectious disease or skin infection or of chronic skin disease (e.g., psoriasis, atopic dermatitis).

19. History of diabetes.

20. Hereditary skin disorders or any skin inflammatory conditions as reported by the volunteer or evident to the MAI.

21. History of significant dermatologic cancers (e.g., melanoma, squamous cell carcinoma) except basal cell carcinomas that were superficial and did not involve the investigative sites.

22. Subject has an obvious difference in skin color between arms or the presence of a skin condition, excessive hair at application site (upper arms), sunburn, raised moles and scars, open sores at application site (upper arms), scar tissue, tattoo or coloration that would interfere with placement of products, skin assessment or reactions to oxybutynin.

23. BMI $\geq$ 30 kg/m^2.

5 PHARMACOKINETICS AND STATISTICAL CONSIDERATIONS

5.1 Study Hypothesis

Heat exposure can enhance the systemic delivery of oxybutynin from the patch and occlusion can enhance systemic delivery from gel. In this study, the influence of standardized heat application on the pharmacokinetics (PK) parameters of oxybutynin will be studied after using Oxytrol® for Women patch. Heat will be applied when the serum levels from the patch reach steady state levels around 24 h indicating steady state skin concentration. A second heat application will determine the influence of heat application on drug reservoir in the skin from the patch. Gel application area will be occluded for three hours. We will test the null hypothesis (H_0) that the coefficient for the patch-by-heat or gel-by-occlusion interaction equals zero, adjusting for time.

5.2 Analyses

Oxybutynin concentrations will be measured in serum samples collected from each subject. Blood samples (approximately 4 mL (0.8 tsp)) will be collected at pre-dosing and then at 24 h, 24 h 15 min, 24 h 30 min, 24 h 45 min, 25 h, 25 h 15 min, 25 h 30 min, 25 h 45 min, 26 h, 27 h, 28 h, 29 h, 30 h, 30 h 15 min, 30 h 30 min, 30 h 45 min, 31 h, 31 h 15 min, 31 h 30 min, 31 h 45 min, 33 h and 34 h 30 min post-patch application. Blood samples (approximately 4 mL (0.8 tsp)) will be collected at pre-dosing and then at 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 7 h 15 min, 7 h 30 min, 7 h 45 min, 8 h, 8 h 15 min, 8 h 30 min, 8 h 45 min, 9 h, 9 h 15 min, 9 h 30 min, 9 h 45 min, 10 h, 10 h 30 min, 11 h, 11 h 30 min and 12 h post-gel application.

Non compartmental analyses (NCA) will be conducted to estimate the PK parameters such as: maximum serum concentration (Cmax), apparent elimination rate constant (k); apparent half-life ($t_{1/2}$), calculated as 0.693/k; $AUC_{0\text{-last}}$ of the serum concentration–time determined by the linear trapezoidal method (patch) and AUC value extrapolated to infinity (AUC_{inf}), calculated as the sum of $AUC_{0\text{-last}}$ and the area extrapolated to infinity: $AUC_{inf} = AUC_{0\text{-last}} + C_{last}/k$ where C_{last} would be the last quantifiable concentration. All NCA analyses will be conducted using Phoenix® WinNonlin® 6.4 (Pharsight, a Certara Company, CA).

5.3 Final Analysis Plan

An objective of this study is to investigate the influence of heat application and occlusion application on the PK parameters of oxybutynin after using patch and gel products. The primary PK parameters to be compared are 1) C_{max}, before and after heat application or occlusion; 2) AUC before and after heat application or occlusion consistent with similar PK studies. [6,7] Determine PK parameters (C_{max}, AUC) of oxybutynin in healthy adults after using Oxytrol® for Women and Gelnique® for the purpose of IVIVC by collecting data over two separate periods. Complimentary *in vitro* data will be collected using human skin.

IVIVC will be conducted comparing PK parameters and profiles to predicted PK parameters and profiles using IVPT results. Multiple methods will be implemented to develop an IVIVC. The first method is to compare the steady state concentrations. The predicted steady state concentration using our current IVPT data will employ the following formula:

$$C_{ss} = \frac{J_{ss} * A}{CL}$$

C_{ss}=steady state serum concentration; J_{ss}=steady state flux; A=area; *CL*=clearance

The second method will compare the PK profiles of the clinical and IVPT study by predicting oxybutynin concentrations at each time point in the IVPT study and comparing it to the clinical PK profile. The third method will be to determine and compare residual patch analysis between in vitro and in vivo.