Determination of the Transdermal Absorption of Chlorpromazine in Pluronic Lecithin Organogel (PLO) Gel in Healthy Adults

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Background
Traditionally, pharmacists have provided compounding services as a component of patient-centered care. Customization of medication doses and dosage forms can assist patients and their caregivers when individualized medication regimens are needed. For patients receiving hospice care, controlling end of life symptoms is essential to maintaining quality of life. Pharmacists who compound frequently create patient specific dosage forms of symptom management medications to be used when swallowing is difficult or impossible due to the life-limiting illness. For example, chlorpromazine (Thorazine®), a conventional antipsychotic/antimanic medication, was commercially available in an oral concentrated liquid at 100mg/mL. Unfortunately, the manufacturer discontinued this oral concentrated liquid product which has been used in hospice for managing terminal delirium, nausea, vomiting, or hiccups. As pharmacists serving on hospice interdisciplinary teams, we now recommend compounding the chlorpromazine oral liquid for convenience of patients and caregivers in medication administration. The compounded formulation at 100mg/ml is concentrated enough that sublingual administration is possible for those patients with swallowing difficulties. Caregiver burden is lifted in that crushing tablets and mixing in applesauce or pudding is no longer needed.

In recent years, there has been an increase in the use of compounded topical gel formulations by hospices to provide an additional route of administration for symptom management medications for their patients. Medications as diverse as chlorpromazine, lorazepam, metoclopramide, morphine, haloperidol, and methadone have been incorporated into topical gels individually and in combination products such as ABH (lorazepam, diphenhydramine, haloperidol) gel. However, published transdermal absorption and bioavailability studies of these topical preparations designed for systemic therapeutic effect has been very limited. In June 2011, Smith et al tested the cutaneous absorption of ABH gel in healthy adults. Their poster discussion presentation concluded that “as commonly used, none of the lorazepam (A) or haloperidol (H) in ABH gel is absorbed in sufficient quantities to be effective in the treatment of nausea and vomiting.”

Therapeutic chlorpromazine concentrations have been determined to be approximately 50-300 ng/ml. Chlorpromazine has variable kinetics and an active metabolite desmethylchlorpromazine. The duration of action has been determined to be between 3-4 hours. The elimination of half-life of chlorpromazine has been determined to be 30 hours in adults. Onset of action of chlorpromazine after oral administration is approximately 30 minutes. The most commonly reported adverse reactions in patients taking chlorpromazine include dizziness drowsiness and orthostatic hypotension.

Transdermal absorption of topically applied medications is dependent on multiple factors:
- Size of drug (less than 500 Daltons)
- Thickness of skin/stratum corneum (avoid callused areas and apply to pulse points)
- Adequate solubility in oil and water
- Concentration gradient adequate to permit passive diffusion

Factors such as low melting point and good solubility in the compounding vehicle improve the stability of the compounded medication.

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Chlorpromazine (MW 355) in pluronic lecithin organogel (PLO gel) has been used to prevent and treat uncontrolled symptoms in hospice patients. PLO gel contains Pluronic F-127 (poloxamer) which is a copolymer of ethylene oxide and propylene oxide. It forms a clear, thermoreversible gel and is most often used as a viscosity-inducing agent for topical gels. Other components are ethoxy diglycol, which is miscible with water and with common organic solvents. It is used as a solvent, solubilizer and cosurfactant and is non-irritating and non-penetrating when applied to human skin. Lecithin, another component of this compound, is used as an emulsifying and solubilizing agent. The last component is isopropyl palmitate which is used as an emollient and thickening agent.

The commonly ordered dose of chlorpromazine gel is 25 mg applied to the inner wrist four to six times daily as needed. Compounded chlorpromazine gel is relatively expensive. The average cost of one milliliter of chlorpromazine gel (100mg/ml) in a topical applicator is approximately $6.00-$8.00 (or, $1.50 per 25mg dose); whereas, commercially available chlorpromazine tablets are $0.55 per 25mg tablet.

Transdermal delivery of chlorpromazine has been studied on various regions of pig skin. The study compared the extent of absorption after passive diffusion and iontophoresis. To ensure adequate absorption of chlorpromazine, iontophoresis was required to help facilitate the movement of drug through the skin. This study demonstrates potential requirements for compounding and application techniques of chlorpromazine to ensure absorption through the skin. There are no current published studies examining the adverse effects of topically applied chlorpromazine. However a compound with similar qualities was studied for tolerability by reviewing reported adverse drug reactions (ADRs) with lorazepam, diphenhydramine, haloperidol, metoclopramide (ABH gel) topical administration (11,181 prescriptions to 8600 hospice patients). A total of 42 ABHR prescriptions (0.4%) were discontinued due to adverse effects. The most frequent ADRs were allergic reaction, agitation, and sedation/somnolence; which occurred 11.9% of the time. Another trial investigated effectiveness of ABH gel and the 3/33 (9%) of patients in two trials reported mild fatigue after using the gel and no patients reported skin irritation.

Significance of Research
The absorption of chlorpromazine individually in PLO gel has not been studied in clinical trials or reported in published literature, resulting in a lack of proof of cutaneous absorption into the blood stream. Patients receiving chlorpromazine in PLO gel may not be receiving the full therapeutic effect of chlorpromazine if it is not absorbed transdermally. Pharmacists in ambulatory care need to make appropriate medication recommendations based on efficacy and safety studies for the benefit of the patients. This is especially true in frail or debilitated patients receiving hospice care. This research will help direct pharmacist recommendations for symptom management, thereby improving treatment outcomes and quality of life for our patients.

Objectives
1. Determine the transdermal absorption of chlorpromazine in PLO gel in healthy adults.
2. Investigate systemic and local adverse effects caused by administration of the study medication.
Evaluation Strategy
The mean plasma concentration (with standard deviation, SD) will be reported at each time point. These mean (SD) concentrations will be displayed graphically. For each patient, plasma concentration AUC (area under the curve) will be calculated using the trapezoidal method. The mean (SD) AUC will be reported. Subject demographics will be summarized as mean (SD) for continuous variables and number and percentage for categorical variables. Subject demographics will be summarized both overall and separately for subjects with and without measureable absorption. Adverse reactions will be summarized as the number and percentage of subjects reporting any ADR, those reporting specific types of ADRs, and those reporting ADRs at each time point.

Methods
This study has been submitted to the Institutional Review Board for approval. Potential participants will complete a consent form and a medical information sheet containing a medication list, drug allergies, and subject demographics. This form will be evaluated by the researcher and volunteers will be included or excluded based on the below criteria.

Inclusion:
- Healthy adult volunteers (18-70 years old) willing to undergo a general health screen (blood pressure, heart rate, respiratory rate, height, weight and temperature) to ensure healthy participants on the study date.

Exclusion:
- Pregnant
- Allergy to phenothiazines, ethoxy diglycol, lecithin, isopropyl palmitate, Pluronic F-127 gel
- Currently taking a phenothiazine medication

Subject requirements for participation in the day of the intervention:
- Subjects must avoid alcohol 24 hours prior to study day
- Subjects must be determined healthy adults upon check-in to the study site
  - Blood pressure less than 140/90mmHg
  - Heart rate between 60-100 beats per minutes
  - Respiratory rate between 14-20 breaths per minute
  - Temperature between 96.4°F and 99.1°F.\(^\text{12}\)

Protocol for the day of the intervention begins when subjects arrive at the study site for check-in. Physical data, including weight, height, and vital signs (blood pressure, heart rate, respiratory rate and temperature) will be recorded after check-in. Female participants will complete a urine pregnancy test.

Protocol for blood draws, gel application and follow-up:
1. The study nurse will draw each subject’s blood at 0 hours according to study protocol and label all blood specimens with the subject’s study identification number.
2. The study nurse will apply a 25mg chlorpromazine gel dose using a topical applicator. Application will be made to the inside of the subject’s wrist in a 5x5 cm area according to an application template.
3. The study nurse will rub the gel into the subject’s skin for one minute with light pressure.
4. The subject will wait in the supervised waiting area and will have blood drawn at 1, 2, and 4 hours after application of the study medication.
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5. The subject will complete an adverse drug effect questionnaire at 1, 2, and 4 hours after application of the study medication.
6. The subjects will be released 15 minutes after the blood draw at 4 hours and will be driven home.
7. The primary investigator will complete a follow-up telephone call for each subject one day after the study date to assess for any delayed adverse reactions.
8. The lab specimens will be handled according to the testing laboratory’s protocol (NMS Labs, 3701 Welsh Road, Willow Grove, PA, 19090).

References
2. Schulz M, Schmoldt A. Therapeutic and toxic blood concentrations of more than 800 drugs and other xenobiotics. Pharmazie 2003:58;447-474.