Chlorpromazine bioavailability from a topical gel formulation in volunteers

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Background Symptom management medications are often compounded into topical gel formulations providing an alternative route of administration for hospice and palliative care patients. Though commonly used, transdermal absorption and bioavailability studies of these gel products are lacking. Chlorpromazine was studied because it is FDA approved for treatment of nausea and vomiting and is used off-label for treatment of agitation and delirium.

Objective The objective of this study is to determine the transdermal absorption of chlorpromazine PLO gel in healthy adults.

Methods Twenty-five milligrams of chlorpromazine in PLO gel was applied to 10 subjects' wrists and 100 mg was applied to 1 subject's wrist. Blood draws were completed preapplication and 1, 2, and 4 hours postapplication. This single-center unblinded study recruited healthy adults between 18 and 70 years of age. Participants were not pregnant, did not have an allergy to any component of the study medication, and were not taking a phenothiazine medication.

Results Chlorpromazine was undetected in any of the 11 subjects' blood samples.

Limitations There is an assumption of equivalent medication absorption in healthy patients and palliative care or hospice patients.

Conclusion Rapid relief of symptoms at end of life is essential. Chlorpromazine in PLO gel may not be an effective treatment option since blood levels were undetectable at 1, 2, and 4 hours after topical application.

In end-of-life care, symptom management may be hindered by the loss of routes of administration as patients decline. Compounded topical gel formulations have been used in an attempt to provide an additional method of delivery. Medications as diverse as chlorpromazine, lorazepam, metoclopramide, morphine, haloperidol, and methadone have been compounded into topical gels individually and in combination products such as ABH (lorazepam, diphenhydramine, haloperidol) gel. These medications are commonly incorporated into a vehicle, such as pluronic lecithin organogel (PLO gel), to enhance transdermal absorption. PLO gel theoretically enhances the absorption of both lipophilic and hydrophilic medications by improving skin permeation.[1]

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Certain compounded topical gel formulations are applied with the goal of transdermal absorption to achieve systemic activity. These medications require specific characteristics in order to be absorbed. Factors influencing the absorption of medications across the skin are the medication's physical characteristics, the thickness of skin/stratum corneum (avoid callused areas and apply to pressure points), and a concentration gradient adequate to permit passive diffusion are factors influencing the absorption of medications across the skin. Desirable physical characteristics of a medication for transdermal absorption are a size of less than 500 g/mol in molecular weight and adequately soluble in oil and water (oil/water partition coefficient of 1-2).[2]

Published observational and transdermal absorption studies of topical preparations designed for systemic therapeutic effect have been limited. Three observational studies have evaluated patient's perceptions of effectiveness of topically administered medications. One group of researchers performed 2 pilot studies about the effectiveness of topical administration of ABH gel. One of the pilot studies found ABH gel applied topically

decreased nausea and vomiting in 74% of patients with chemotherapy induced nausea and vomiting.[3] The second pilot study reported a drop in the mean nausea and vomiting score after topical administration of ABH gel in patients receiving chemotherapy.[3] Moon describes 4 patient cases where ABH gel relieved nausea and vomiting in patients admitted to hospice with cancer or failure-to-thrive diagnoses.[4]

While there were known limitations to the observational studies, topical administration of these medications has become common practice within palliative care. Smith et al tested the cutaneous absorption of ABH gel in healthy adults. Their discussion concluded that none of the lorazepam (A) or haloperidol (H) was absorbed into the blood stream. In addition, diphenhydramine (B), though detectable by the lab, had insufficient quantities to be effective in the treatment of nausea and vomiting.[5] A study examined the transdermal absorption of topically applied morphine in healthy adults. After topical morphine administration, no quantifiable morphine plasma concentrations were detected.[6] Sylvester et al studied the serum concentrations of methadone after oral and topical administration. It was determined that 18 of 20 serum methadone concentrations after topical administration were less than 10 ng/mL; 1 subject receiving the highest dose topically peaked at 25.8 ng/mL. These blood concentrations are considerably lower than serum concentrations after oral methadone administration ranging 62 to 393 ng/mL.[7]

Topical application of chlorpromazine in PLO gel is a commonly used preparation to relieve the symptoms of nausea, vomiting, restlessness, and agitation. The physical characteristics of chlorpromazine include a molecular weight of 350 g/mol and an oil/water coefficient of 5.3.[8] When comparing these characteristics to an ideal medication for transdermal absorption, chlorpromazine may potentially be absorbed after topical application. To date, no studies investigating chlorpromazine transdermal absorption in humans have been published. An in vitro study of the transdermal delivery of chlorpromazine compared the extent of absorption after passive diffusion and iontophoresis across pig skin. Iontophroesis is a technique utilizing mild electric current to enhance skin penetration of medications. The results of the study demonstrated that passive diffusion produced no absorption of chlorpromazine and iontophoresis was required to help facilitate the movement of chlorpromazine through the pig skin.[9]

Patients receiving chlorpromazine in PLO gel may not achieve a clinical response if it is unabsorbed transdermally. To evaluate topical administration of chlorpromazine in PLO gel, our study's primary objective is to determine transdermal absorption. Since studies investigating the adverse effects of chlorpromazine in PLO gel are also lacking, the secondary objective is to identify any systemic and local adverse effects caused by administration of chlorpromazine in PLO gel. This research will help direct symptom management decisions, improve treatment outcomes, and patient quality of life.

TABLE 1 General health screen criteria

Measurement	Value
Weight	> 110 pounds
Height	No limit
Blood pressure	90/60 mmHg > x < 140/90 mmHg
Heart rate	60-100 beats per minute
Respiratory rate	14-20 breaths per minute
Temperature	96.4-99.1°F

Methods

Study subjects

The study protocol was approved by the Institutional Review Board of The Ohio State University. All subjects provided written informed consent prior to enrollment in the study. Adult volunteers (18-70 years old) enrolled in the study were willing to undergo a general health screen and were aware that they would receive chlorpromazine topical gel.[10] The general health screen criteria are noted in Table 1. Subjects were excluded if they were either pregnant (determined by pregnancy test on day of study); had an allergy to chlorpromazine, lecithin or Pluronic F-127 gel; or were currently taking a phenothiazine medication. Subjects were required to abstain from alcohol for 24 hours prior to study initiation.

Study drug preparation and administration

A baseline blood draw was completed to ascertain the absence of chlorpromazine in each subject's blood before application of the medicated gel. A local compounding pharmacy prepared chlorpromazine in PLO gel according to a commonly utilized recipe. Each product was visually inspected by the pharmacist for accuracy and consistency and was appropriately labeled as a prescription for research. The final concentration of the gel was 100 mg/mL and required a dose of 0.25 mL to attain a 25 mg dose. All study subjects were provided access to fluids throughout the study day and skin was assessed to ensure adequate hydration. All chlorpromazine PLO was applied by a registered nurse to intact skin on the inner surface of the wrist in a 5 x 5 cm area. The wrist was chosen to be consistent with the Smith et al recent ABH publication; in addition, the wrist is the number one reported site of application by hospice programs.[5] Ten subjects received a

TABLE 2 Patient characteristics

Subject no.	Age (Years)	Sex	Weight (pounds)	Height (inches)	Body mass index
1	54	M	250	71	34.9
2	64	M	170	72	23.1
3	51	F	156	65	26.0
4	27	F	141.5	66	22.8
5	28	M	208	72	28.2
6	26	F	135	67	21.1
7	24	F	160	64	27.5
8	27	F	117	63	20.7
9	23	M	185	69	27.3
10	28	M	173	68	26.3
11	26	F	114	64	19.7
Mean ± SD	**34.40 ± 14.5**	**N/A**	**164.5 ± 40**	**67.4 ± 3.3**	**25.2 ± 4.4**

25 mg dose of chlorpromazine in PLO and 1 subject received 100 mg. The study nurse applied the medicated gel and massaged the area with light pressure for 1 minute to assist absorption of gel into the subject's skin. Serial blood draws were completed at 1, 2, and 4 hours after the application of chlorpromazine.

Safety monitoring

Vital signs (blood pressure, heart rate, respiratory rate and temperature) were collected at baseline and 1, 2, and 4 hours postapplication of chlorpromazine. Normal levels are detailed in Table 1. Each subject completed an adverse-effect questionnaire at baseline, and 1, 2, and 4 hours after the application of chlorpromazine to monitor for local and systemic adverse effects of chlorpromazine. The questionnaire was modified from the Division of Microbiology and Infectious Disease (DMID) Adult Toxicity Table and used a grading system from 1 (mild, not requiring treatment) to 4 (life-threatening, requiring hospitalization). Systemic adverse effects mentioned in the questionnaire included fatigue, headache, sensation impairment, and dizziness.[10] The primary investigator initiated follow-up phone calls to each subject 24 hours after medication application to assess for delayed adverse effects utilizing the adverse effect questionnaire.

Chlorpromazine assay or analytical methods

Analysis by gas chromatography for chlorpromazine was performed at NMS Labs (Willow Grove, PA). In summary, an internal standard (8-methoxyloxapine) was added to 1.0 mL whole blood aliquots that were pH adjusted with 10% NaOH and extracted with H2O/isopropanol, petroleum either and methylene chloride. The solvent layer is then pipette into another tube containing dilute HCl. The bottom acid layer was then pipette into another tube, made basic with 5% NaOH, and back extracted with methylene chloride. Chlorpromazine was analyzed on a DB-17 capillary column using an Agilent 6890 Gas Chromatograph with nitrogen selective detection (GC/NPD). This GC/NPD method was calibrated over a range of 10 to 1000 ng/mL, with inter-assay precision for chlorpromazine of 10.50% and 7.73% at 100 and 500 ng/mL, respectively. Elution time was approximately 7.7 minutes for chlorpromazine.

Statistical analysis

Descriptive statistics were calculated to determine the mean and standard deviation of subject demographics. Adverse effects were also reported.

Results

A total of 5 males and 6 females who were 34.4 (SD ± 14.5) years of age and had body mass indexes of 25.2 (SD ± 4.4) participated in this study. Characteristics of the study subjects are detailed in Table 2.

No quantifiable chlorpromazine concentrations were achieved in any blood samples before and after topical administration of chlorpromazine 25 mg or 100 mg in PLO gel. Subject 7 withdrew from the blood draw at hour 2 due to difficulty with blood collection. However, subject 7 managed to successfully provide a blood sample at hour 4. Because the topical administration of chlorpromazine produced no measurable concentrations, it was impossible to calculate a mean or standard deviation for concentrations of chlorpromazine at each time point.

TABLE 3 Adverse effects

Adverse effect	Subject number	Grade[a]	Time point
Fatigue	2	1	2 hours
	2	1	4 hours
	9	1	1 hour
	9	1	2 hours
Headache	3	1	0 hour
	3	1	1 hour
	4	1	2 hours
	4	2	Follow-up
Sensation Impairment	4	1	1 hour
	9	1	1 hour
	9	1	2 hours

[a] Grade 1 is a mild symptom not requiring treatment, Grade 2 is mild to moderate symptom with minimal medical therapy required, Grade 3 is marked limitation in activity with medical therapy required, Grade 4 requires hospitalization.[11]

The subject receiving 100 mg of chlorpromazine reported a grade 1 rash described as a few red spots in the area of gel application. In addition, 4 subjects reported various systemic adverse effects as seen in Table 3. Fatigue and sensation impairment, occurring in 2 subjects, were given a grade of 1 (mild) and did not require treatment. Out of the 2 subject's reporting headache, 1 subject reported during the follow-up adverse effect questionnaire a grade 2 headache that required treatment. There were no considerable differences in the vital signs for all subjects between all time points.

Discussion

There has been an increased use of medications compounded into PLO gel for symptom management. Chlorpromazine in PLO gel has been used to relieve nausea, vomiting, agitation and delirium with no clinical trials determining the transdermal absorption of the compound. This study determined the transdermal absorption of chlorpromazine in PLO gel in healthy adults. It was not the purpose of this study to determine efficacy of chlorpromazine in PLO gel to relieve symptoms.

According to the laboratory analysis, chlorpromazine was unquantifiable in any blood samples from the 11 subjects. The laboratory test for the presence of chlorpromazine is able to detect levels greater than 10 ng/mL of chlorpromazine in blood. The reported therapeutic range of chlorpromazine has been determined to be 50-300 ng/mL.[12] Chlorpromazine concentrations less than 10 ng/mL or undetectable could be considered as subtherapeutic. Since chlorpromazine in PLO yielded no systemic blood concentrations at a therapeutic level for doses of 25 mg and 100 mg, it was determined that chlorpromazine in PLO may be unsuitable for use to treat uncontrolled symptoms.

Numerous studies investigating compounded topical medications have utilized the inside of the wrist as the site of medication application.[4-7] Compounded topical medications, such as ABH, chlorpromazine and metoclopramide, are applied to a patient's inner wrist in clinical practice to relieve symptoms. Although this site is commonly utilized, areas of the skin may be more permeable to medications than the inner wrist. These areas include the face/head, chest/back, buttocks, abdomen, and upper arms/legs.[13]

Adverse effects reported with oral or intravenous chlorpromazine are dizziness, drowsiness and orthostatic hypotension.[14] Although 4 subjects reported fatigue, headache, or sensation impairment, the concentrations of chlorpromazine in each subject's blood were undetectable. Therefore, outside factors may have influenced the occurrence of these adverse effects. Contributing factors to the reporting of adverse effects may include the time and duration of study, the study environment, or frequency of blood draws.

The results of this study are consistent with results of the ABH, morphine and methadone trials.[5-7] These investigations have yielded results of limited absorption of diphenhydramine and methadone; meanwhile, no absorption of lorazepam, haloperidol, morphine and chlorpromazine was detected after topical administration. Since case reports have described benefit of these topically applied medications, the efficacy may not be due to the medications' pharmacologic effects, but from other mechanisms.

Three subjects reported a relaxing and calming effect during the 1-minute topical application of chlorpromazine. The inner wrist is an acupressure point on the body known as the master of the heart (MH6) and is recognized by the National Institute of Health in its position paper on acupressure in 1997.[15] Wright studied acupressure with motion sickness bands (MSB) applied to the wrist to control nausea and vomiting in patients admitted to hospice. A decrease in self-reported nausea symptoms within an average of 1 hour after the intervention was reported in 29 out of 33 patients.[16] A pilot study by Perkins showed patients receiving acupressure with an MSB required less frequent dosing of rescue antiemetics, experienced fewer episodes of vomiting, and were less likely to require an increase in scheduled antiemetics.[17] Topical administration may improve the patient's symptoms through a placebo effect and indirectly via acupressure.

The placebo effect is believed to occur from patients' expectancy and conditioning to a response as a result of verbal suggestions and past experiences.[18] One study found that patients' awareness of treatment administration seemed to influence their report of effectiveness.[19] The patient's positive experience of the clinical encounter may augment the pharmacological effects of the medication.[20]

Health care professionals using a warm, friendly manner and active listening with empathy improve the patient-practitioner relationship. These techniques are commonly utilized by hospice and palliative care clinicians. A study compared the improvement of symptoms in 3 groups of patients with irritable bowel syndrome, an observational group, a placebo acupuncture alone group, and placebo acupuncture with a patient-practitioner relationship. Patients reported greater improvement in symptom control in the group receiving the patient-practitioner relationship.[21]

The lack of systemic absorption of topical chlorpromazine when applied to the inner wrist indicates that topical administration of this medication may not correlate with the systemic absorption needed to effectively manage symptoms at end of life. When prescribed, the trusting patient-practitioner relationship may contribute to the perceived efficacy of topical medications. In addition, the application of the gel may invoke an acupressure-like response and assist in the relief of the patient's symptom.

It is important to consider the individual patient when deciding if compounded topical medication is appropriate for use. Evaluating other potential treatment options and the evidence-based literature is essential to treating the patient's symptoms effectively. Main points to address when considering the use of a compounded medication include evaluating previously failed drug therapies and other commercially available treatment options; and requesting evidence-based literature for compounded dosage forms and written information on formulations.[22] The use of compounded topical chlorpromazine in PLO gel was unabsorbed at either 1, 2, or 4 hours after topical application and therefore may not produce systemic blood levels currently studied to reduce symptoms. The results of this study will assist in directing recommendations against the use of chlorpromazine in PLO gel applied to the wrist and towards evidence-based treatment modalities for symptom management. Further research is needed to determine the proper use and location of application for compounded topical medications at end of life.

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