Brief Report

ABH Gel Is Not Absorbed From the Skin of Normal Volunteers

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Abstract

Background. Lorazepam (Ativan®), diphenhydramine (Benadryl®), haloperidol (Haldol®) (ABH) topical gel is currently widely used for nausea in hospice because of perceived efficacy and low cost and has been suggested for cancer chemotherapy. However, there are no studies of absorption, a prerequisite for effectiveness. We completed this study to establish whether ABH gel drugs are absorbed, as a prerequisite to effectiveness.

Intervention. Ten healthy volunteers, aged 25 to 58 years (mean 37 years), two African Americans and eight Caucasian Americans, applied the standard 1.0 mL dose (2 mg of lorazepam, 25 mg of diphenhydramine, and 2 mg of haloperidol in a pluronic lecithin organogel), rubbed on the volar surface of the wrists by the subject.

Measures. Blood samples were obtained at 0, 30, 60, 90, 120, 180, and 240 minutes. Plasma concentrations were analyzed by liquid chromatography-tandem mass spectrometry using deuterated internal standards for each drug.

Outcomes. No lorazepam or haloperidol was detected in any sample from any of the 10 volunteers down to a level of 0.05 ng/mL. Diphenhydramine was found in multiple plasma samples at concentrations >0.05 ng/mL in three patients, with the highest concentration of 0.30 ng/mL in one person at 240 minutes. Overall, five of 10 patients exhibited detectable diphenhydramine in one or more samples, supporting limited absorption. No subject noted any side effects.

Conclusions/Lessons Learned. As commonly used, none of the lorazepam, haloperidol, or diphenhydramine in ABH gel is absorbed in sufficient quantities to be effective in the treatment of nausea and vomiting. Diphenhydramine is erratically absorbed at subtherapeutic levels. The efficacy of ABH gel should be confirmed in randomized trials before its use is recommended. J Pain Symptom Manage 2012;43:961–966.

Key Words

Palliative care, nausea, topical drug, absorption

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Introduction

Many cancer patients suffer with nausea and vomiting yet cannot swallow drugs. Nausea and vomiting account for 18% of palliative care consultations at cancer centers.[1] Many patients and families either are not offered or will not accept treatment via the rectal route.[2] If there is no way to give oral drugs and no accepted alternative, an intravenous (IV) or subcutaneous delivery system must be used. The impact of the antiemetic delivery system is important for the following reasons. First, an IV or subcutaneous line increases cost of care by $280, as it requires skilled nursing. Second, if the patient must be admitted as a result of uncontrolled nausea and vomiting, each admission costs more than $2500/day at the Virginia Commonwealth University (VCU) Health Systems. Finally, unrelieved nausea increases the suffering of both the patient and the family. The U.S. now spends two times more than any other country on oncology care, mostly for palliative chemotherapy, supportive care, and end-of-life care,[3] and better palliative care is one critical component to improved care and cost control.[4] Last-year-of-life expenses constituted 22% of all medical, 26% of Medicare, 18% of all non-Medicare, and 25% of Medicaid expenditures.[5] Medicare now spends 9% of all expenditures in the last month of life.[6] One way to reduce the cost of care while maintaining quality is to use less expensive drugs, but only if they work.[4]

The cutaneous approach for drug delivery has many advantages including simplicity, ease of application and dose adjustment, stability, and inexpensive generic drugs. Lorazepam (Ativan®), diphenhydramine (Benadryl®), haloperidol (Haldol®) (ABH) gel costs pennies per dose, less than ondansetron and topical granisetron (Sancuso®, $285.00 per five-day patch). ABH gel may have shown some efficacy in nausea and vomiting in uncontrolled trials[7] of 2 mg of lorazepam, 25 mg of diphenhydramine, and 2 mg of haloperidol in pluronic lecithin organogel, an inactive vehicle.[8] In a trial of 23 patients, 17 (74%) said the gel decreased their nausea from a score of 4 ± 1.0 to 2 ± 1.7 (on a scale of 0 = no nausea to 5 = worst possible nausea), and 16 (70%) had relief of vomiting ($P < 0.0001$). However, nausea was assessed by a telephone call at the end of the month of treatment, not by prospective testing, and patients were allowed to use other antinausea drugs. In a subsequent trial, 10 of 10 chemotherapy patients reported that ABH gel was effective, and the mean nausea score decreased from 6.1 ± 2.99 (scale of 0−10) to 1.7 ± 2.0 30 minutes after application ($P < 0.0005$); again, other antiemetic use was allowed and there was no control group. No side effects were reported by any patients. Neither of these trials measured absorption of the drugs. There have been no other evaluations of effectiveness except case reports.[9] The use of ABH gel in community practice is widespread despite the lack of evidence; Weschules[10] reported that 76% of 8600 hospice patients received 6529 topical gel ABH prescriptions, and ABH is on the formulary of most local hospices.

We do not know which of the drugs are absorbed, if clinically important systemic levels are achieved, if the combination is important, or if this is a placebo effect. In clinical trials, there may be a 30% to 40% response of nausea to placebo,[11] as well as regression to the mean, response frame shift, and use of other drugs. If ABH gel works, it is an important inexpensive therapy that should be tested in other situations such as chemotherapy-induced emesis. If it does not work, palliative care and hospice oncology patients are using an ineffective therapy when they could be using proven therapies.[12] This needless suffering will cause some avoidable and costly hospitalizations. We performed this study to establish if ABH gel drugs were absorbed as a prerequisite to effectiveness.

Methods

Study Subjects

We measured the absorption of the three components in the topical ABH gel in 10 healthy volunteers and determined if there were any adverse effects. The topical ABH gel was prepared by the VCU Investigational Drug Pharmacy as described by Bleicher et al,[7] and consisted of lorazepam 20 mg, diphenhydramine 250 mg, haloperidol 20 mg, lecithin organogel 2 mL, ethoxydiglycol 0.83 mL, water 0.2 mL, and pluronic gel 20% (quantity sufficient to make 10 mL). A 1 mL volume of ABH gel was applied to the volar