The Use of Transdermal ABHR for Nausea/Vomiting, Agitation, and/or Anxiety in Hospice Patients

Tracey Gordon, B.S. Pharm, Pharm D.

Nausea, vomiting, agitation, and anxiety are common symptoms found in hospice patients approaching end-of-life. The use of Transdermal ABHR (Ativan, Benadryl, Haldol, and Reglan) has become a popular alternative approach for patients who have barriers to taking these medications orally or rectally. In this article, the literature evaluating the absorption and effectiveness of the ABHR transdermal product will be reviewed.

While there are many internet articles from reputable sites (examples to follow) that support the use of transdermal ABHR, many articles reference studies that may yield misleading conclusions. For example, Lohr et al (1) published an article in HemOnc today. It referenced two studies supporting the use and effectiveness of ABHR transdermal. However, the first article that was referenced only looked at the tolerability of ABHR in many different dosage forms. To expand upon the purpose of the study that was referenced, Weschules et al (2) examined the incidence of adverse drug reactions (ADRs) associated with ABHR gel/suppositories/PO caps and suspensions in hospice patients. This evaluation of 8600 patients found an overall 0.5% discontinuation rate of ABHR gel due to side effects. In patients >64 yrs old, the most common reason for discontinuation rates were as follows: 10.7% because of increased agitation, restlessness and confusion; 7.1% due to hallucinations, and 3.6% due to constipation and nausea/vomiting. In addition, the most frequent reasons for discontinuation for all age groups were agitation, sedation/somnolence and allergic reaction (which included, but were not limited to lethargy and hypotension). However, this study did not evaluate the efficacy or absorption of ABHR in any dosage form, but only how well ABHR gel was tolerated.

Continued on page 2

Lidoderm now available as generic: a review of the brand to generic drug approval process.

Maria Castano, PharmD

The FDA approved Watson Pharmaceutical’s generic form of Lidoderm® (lidocaine 5% topical patch) on August 23, 2012, and it was shipped to manufacturers starting in September 2013. You may be asking why it took so long. The answer is that there are laws that regulate when and how a generic medication is launched in the US.

When a new drug is being developed, the pharmaceutical manufacturer obtains a patent for the new chemical entity. This patent provides the pharmaceutical company with 20 years of protection from generic competition, and allows the company to recoup the cost of drug development. After this period, a generic manufacturer may file an ANDA (abbreviated new drug application) with the FDA in order to produce the generic version of the original drug. Once approved, the generic manufacturer is awarded a 180-day period of exclusivity. This exclusivity is an incentive for generic manufacturers to be the first to have their generic product approved, with the idea that this will reduce the cost of medications for the public. The reality, however, is the cost of the generic version is still relatively high during this period of exclusivity due to the lack of competition from other generic manufacturers.

For example, the average cost of brand Lidoderm patches is $312.01 for a box of 30 patches, compared with $269.58 for the same amount of generic lidocaine patches manufactured by Watson. This small difference in cost is typical of newly-approved generics. The price of the generic will likely decrease as more generics become available.

Continued on page 3
Use of Transdermal ABHR, continued from page 1

The second study Lohr referenced to support the use ABHR transdermal was published by Bleicher et al (3) in the Journal of Supportive Oncology. Bleicher et al, critiqued two pilot trials: The first involved 23 patients and the second included 10 patients. All patients were given prescriptions for lorazepam 2mg/ml, diphenhydramine 25mg/ml, and haloperidol 2mg/ml gel 0.5ml topical every 6 hours as needed for breakthrough nausea/vomiting. Both trials concluded statistically significant decrease in breakthrough nausea and vomiting. However, all patients remained on prophylactic anti-nausea/vomiting therapy which included one or more of the following medications: Zofran, Kytril, Emend, Anzemet, Aloxil, tropisetron (not available in the US), and/or dexamethasone. The incidence of nausea/vomiting was assessed by a telephone call at the end of the month of treatment, not by prospective testing. In addition, there were no control groups, and all patients were on one or more of the above prophylactic anti-nausea medications. Neither of these trials measured absorption of the drugs, which brings up the question of what the treatment effect may have been.

Based on the evidence in both trials, we do not know which drug was absorbed, if clinically important systemic levels are achieved, if the combination is important, or if this is a placebo effect. To understand the power of placebo, Hardy et al (5), conducted a study regarding the effectiveness of opioid induced nausea/emesis and emesis in cancer patients. This study was a double-blind, randomized parallel group comparing Reglan 10mg po TID, Zofran 24mg po daily and placebo. They found no statistically significant difference between the groups regarding complete control of emesis or nausea. In addition, according to Glare et al (4), in many clinical trials there may be a 30% to 40% response of nausea to placebo.

Another example of a potentially “misleading” claim could be found in a popular pharmacy trade magazine which published an article stating, “A host of articles and case reports have been published to demonstrate the effectiveness of this particular combination as well as several similar preparations (6).” However, the above article referenced Moon et al (7) as their source to make these claims. Moon et al (7) stated, “ABHR gel-has proven highly effective.” It also stated, “This gel is an option that has proven highly effective for relieving the symptoms of nausea and vomiting for terminally ill hospice patients. (7)”. They reported that many of the patients were taking other anti-emetics (ie compazine, haldol and/or zofran), but these conclusions were not based on controlled studies, but rather on observations and case reports only. Again, there were no control groups and absorption was not studied.

A literature review revealed only one study that addresses the absorption of these meds through the skin. Smith et al (7) looked at the absorption of ABH gel through the skin of normal volunteers. This study used a 1ml dose of lorazepam 2mg/ml, Benadryl 25mg/ml and Haldol 2mg/ml applied to the skin. Blood samples were drawn at 0, 30, 60, 90, 120, and 240 minutes. Plasma concentrations were analyzed by liquid chromatography. The results revealed the absence of lorazepam and haloperidol detected in any sample down to a level of 0.05ng/ml. However, diphenhydramine was found in multiple plasma samples at low concentrations in some of the patients. In conclusion, none of the lorazepam, haloperidol or diphenhydramine in ABH gel was absorbed in sufficient quantities to be effective in the treatment of nausea/vomiting and diphenhydramine was erratically absorbed at subtherapeutic levels in that trial. This may explain Weschules (2) findings of the most frequent ADR’s of ABHR gel that included sedation/somnolence, lethargy, hypotension, constipation and confusion. In addition, the malabsorption may explain the ADR’s of agitation, hallucination, restlessness and confusion.

In conclusion, there are many reputable sources making positive statements regarding the efficacy of ABHR transdermal. We should bear in mind the sources of these conclusions and the potential power of a placebo effect. Since the only study found looking at the absorption of ABH topical revealed a small percent of Benadryl was absorbed through the skin of normal volunteers, administration of these medications either by the oral route, crushed or SL, or rectally is best for optimal therapeutic efficacy and cost-effectiveness. More double-blind, placebo controlled studies should be performed before routine use of ABH gel/cream is utilized in hospice patients.

References shown on page 4
FDA to complete phase-out of chlorofluorocarbon inhalers.

The U.S. Food and Drug Administration will complete its phase-out of all inhaler medical products containing chlorofluorocarbons (CFCs) by Dec. 31, 2013. This effort is to comply with an international treaty to protect the ozone layer by phasing out the worldwide production of numerous substances, including CFCs, which contribute to ozone depletion.

While most inhaler products containing CFCs have already been phased out by the FDA, two products currently remain on the market: Combivent Inhalation Aerosol and Maxair Autohaler. However, these products will no longer be available after the end of this year. People with asthma or chronic obstructive pulmonary disease (COPD) who use these inhalers should talk to their health care professional about a prescription for an alternative treatment.

Combivent Inhalation Aerosol will no longer be available after July 2013. It contains two medicines—ipratropium bromide and albuterol sulfate. A bronchodilator intended to open airways, it is approved for patients with COPD. An alternative inhaler—Combivent Respimat—contains the same two medicines but does not contain CFCs. It was approved by the FDA in 2011. The same two active ingredients are also available in the nebulized formulation, Duoneb, which is the most cost-effective alternative to the metered-dose inhaler and preferred at end of life.

Maxair Autohaler will not be available after Dec. 31, 2013. This inhaler contains pirbuterol, which is also a bronchodilator and is used for the treatment of bronchial spasms in patients with asthma or COPD. Alternative inhalers are available that contain other bronchodilator medicines, such as albuterol, but do not use CFCs as a propellant to move the medicine from the inhaler. Albuterol is also available in numerous strengths as a nebulizer formulation and preferred at end of life.

References:


Hydrocodone: new product formulations and potential schedule changes.

Hydrocodone Extended-Release (Zohydro ER)²

The U.S. Food and Drug Administration approved on October 25, 2013, Zohydro ER (hydrocodone bitartrate extended-release capsules) for the management of pain severe enough to require daily, around-the-clock, long-term treatment and for which alternative treatment options are inadequate. Zohydro ER, a Schedule II controlled substance under the Controlled Substances Act, is the first FDA-approved single-entity (not combined with an analgesic such as acetaminophen) and extended-release hydrocodone product.

Proposed Hydrocodone Reclassification³

On October 24, 2013 Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research at the FDA released a statement highlighting a proposal to change hydrocodone containing products, such as Vicodin from schedule III to schedule II, similar to other narcotic pain relievers such as morphine or oxycodone.

“By early December, FDA plans to submit our formal recommendation package to HHS to reclassify hydrocodone combination products into Schedule II. We anticipate that the National Institute on Drug Abuse (NIDA) will concur with our recommendation. This will begin a process that will lead to a final decision by the DEA on the appropriate scheduling of these products.”

Use of Transdermal ABHR, continued from page 2

1. Lohr, LK. ABHR gel for refractory nausea and vomiting. HemOnc Today; www.hemonctoday.com, April 25, 2010
6. Shannon W. Fields, BA, CPhT. Meeting the Needs of the Hospice Patient. Pharmacy Times; Published Online: Friday, June 1, 2007

Follow us on Twitter! (@PHCpharmacy).

Follow us on Twitter to keep up with the latest clinical news and regulatory trends that affect hospice care, or share your own exciting story!