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Medications: A Hidden Source of Gluten

by Vanessa Maltin, Aline Charabaty, Robert Mangione

Celiac disease is a chronic autoimmune digestive disease characterized by inflammation and destruction of the small bowel mucosa after it has been exposed to gluten in genetically predisposed individuals. Gluten is the storage protein in wheat, rye and barley. Although food is generally thought to be the primary source of gluten intake, medications are a hidden source of gluten that can cause potentially long-term intestinal damage and exacerbate celiac symptoms. The Food Allergen Labeling Consumer Protection Act of 2004 requires packaged food labels to name all ingredients containing wheat and other common allergens. No similar requirements exist for medications, leaving physicians, pharmacists and patients with limited access to information about gluten in medications.

INTRODUCTION

According to the National Institutes of Health, approximately three million Americans are believed to have celiac disease, an autoimmune enteropathy triggered by the consumption of gluten in genetically predisposed individuals. In patients with celiac disease, exposure of the small bowel to gluten results in an immunologically mediated inflammatory reaction that damages the small bowel villi. The hallmark of the disease is villous atrophy, leading to the malabsorption of nutrients and vitamins. The classical symptoms of celiac disease include abdominal pain, diarrhea, bloating and steatorrhea (Table 1). Nutrients

and vitamins malabsorption can lead to failure to grow in children, weight loss in adults, iron deficiency anemia, neurological disorders, osteoporosis and coagulopathy. Extra-intestinal manifestations of celiac disease include arthritis, hyposplenism and dermatitis herpetiformis. Untreated celiac disease can have far reaching consequences, including an increased risk of gastrointestinal cancers and Non-Hodgkin's lymphoma, as well as a deleterious effect on women's reproductive health.

The only treatment for celiac disease is a lifelong strict gluten-free diet (1). Gluten is the storage protein of wheat, rye and barley. Because ingesting even the smallest amount of gluten can damage the small bowel and exacerbate celiac symptoms, it is very important to avoid any gluten ingestion. This becomes a problem when considering the many hidden sources of gluten. These include gluten used as an emulsifier and stabilizer in prepared food (e.g. non-dairy creamer, soy sauce, soup, candy, etc.), gluten in cross-contaminated cooking utensils, and gluten used as an excipient in medications.

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A PATIENT’S PERSPECTIVE

Heidi Collins is a CNN news anchor. Everyday from 9 A.M. until Noon EST she is on air informing the world about the latest news. She is known for her journalistic prowess, her ability to eloquently articulate the news to her viewers and for offering profound insight in to all things domestically and internationally that are newsworthy. Despite her incredible talents, on Christmas Eve 2006 Heidi was at a loss. Her six-year-old son Riley was in the emergency room with a 104-degree fever and a raging infection. The doctors said he needed antibiotics, but Riley has celiac disease and no one could answer Heidi’s first question: is it gluten-free?

The doctors and nurses didn’t know. The pharmacist didn’t know. So, they did the next most logical thing. They called the drug manufacturer. Promptly they received a recording wishing them a happy holiday season and informing them that they would reopen at a later time. Heidi then pulled out her cell phone and called the National Foundation for Celiac Awareness (NFCA). Luckily, one staffer had her phone forwarded to her cell phone just in case someone called in with an emergency. She was able to give Heidi some advice for medications, such as using an intravenous antibiotic. Using this information, Heidi and the doctors decided to give Riley the antibiotics to cure the infection.

But the questions still remain. What happens if a patient with celiac disease takes a medication that contains gluten? What are the long-term consequences? How can a medical practitioner determine if a pill contains gluten if it is not on the label?

FOOD ALLERGEN LABELING CONSUMER PROTECTION ACT OF 2004

To assist patients with managing the diet, the Food Allergen Labeling Consumer Protection Act of 2004 (FALCPA) required packaged food labels to name all ingredients containing wheat and other common allergens. The law mandates specific label declarations of major food allergens for all FDA-regulated foods labeled on or after January 1, 2006 with the exception of raw agricultural commodities, ingredients that are specifically exempt from the definition of a major food allergen and highly refined oil derived from one of the allergens.

Table 1
Symptoms of Celiac

- Abdominal Pain
- Chronic Diarrhea
- Dermatitis Herpetiformis
- Seizures
- Ataxia
- Infertility
- Depression

A major food allergen is defined as a food ingredient that contains protein derived from milk, egg, fish, crustacean shellfish, tree nuts, wheat, peanuts or soybeans. Allergens must be listed in plain language within the ingredient list or via the “Contains” followed by the name of the allergen or in a parenthetical statement in the list of ingredients (2). To prevent confusion, the plain language version must use the same name as the allergens (3). A fictional example is provided in Figure 1.

Although the initial law did not include a definition for gluten-free foods, the FDA is expected to issue a rule in August 2008 that will define the term gluten-free for voluntary use in the labeling of foods. The ruling is expected to define gluten-free to mean that the food product does not contain any of the following:

An ingredient that is any species of the grains wheat, rye, barley, or a crossbred hybrid of these grains (all noted grains are collectively referred to as “prohibited grains”); an ingredient that is derived from a prohibited grain and that has not been processed to remove gluten (e.g., wheat flour); an ingredient that is derived from a prohibited grain and that has been processed to remove gluten (e.g., wheat starch), if the use of that ingredient results in the presence of 20 parts per million (ppm) or more gluten in the food; or 20 ppm or more gluten (4).

FALCPA was a major landmark for patients with celiac disease and food allergies providing consumers with access to important information about the food they are eating. Yet no similar requirement exists for medication labels.

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Figure 1.

THE PROBLEM WITH MEDICATIONS

Common excipients used in medications include cornstarch, potato starch, tapioca starch, *wheat starch* (gluten), modified starch, pregelatinized starch and pregelatinized modified starch. An excipient (e.g., a tablet or a capsule) is the inactive substance used as a carrier for the active ingredient of a drug. It allows the packaging of large doses of active ingredient and stabilizes the active ingredient, ensuring an adequate shelf life of the product. The excipient also facilitates the administration and absorption of the medication. In addition, inert materials may be used in the manufacturing of tablets to enhance the product’s processing and compression characteristics (i.e. diluents, binders and glidants and lubricants). Some excipients may also be used to enhance the physical characteristics of the tablet (i.e. disintegrants, colors, favors, sweetening agents, etc.). A capsule may contain the active ingredient(s) that has been mixed with a diluent such as lactose to achieve greater bulk before it is placed into a capsule (5).

There are several issues pertaining to medications and celiac patients, related to the inadequate labeling of ingredients in a product and the suboptimal awareness of the importance of gluten-free medication for patients with celiac disease.

There are currently no requirements for the labeling of gluten or other common allergens found in drug ingredients and no specific warning on the label for individuals with celiac disease. Moreover, botanical source of starch may not be specified on the drug label. Another source of confusion (and frustration) for the patient is the fact that the nature of the excipients can

differ between the generic formulation and the brand-name drug. Last, but not least, potential sources of gluten and the potential harm from ingesting gluten are not always well recognized by health care professionals (treating physicians and pharmacists)(6).

Another important issue to consider is whether or not prescribed medications are getting adequately absorbed by the damaged small bowel in patient with untreated celiac disease or in patients with only partially healed small bowel mucosa (e.g. early after initiating gluten-free diet). A review of the literature shows a lack of studies evaluating this important question. There are few case reports (Alzahrani AS, Al Sheef M. *Endocr Pract*, 2008;14(3):347-350) of lack of response to the oral administration of suprapharmacologic dose of vitamin supplement in patient with unrecognized/untreated celiac disease. Whether this translates to the poor absorption of (and hence, poor response to) any medication, such as an antibiotic or antihypertensive drug, is not known, but should definitely be considered.

HOW TO HELP PATIENTS WITH MEDICATIONS

The first step to determine what excipient is used in a medication is to look at the package insert. Look for the word starch. Cornstarch can be considered gluten-free. However, most packages only list the word starch without listing a source.

In fact, a recent search of *DailyMed Rx Labeling* conducted by the American Society of Health-System Pharmacists on March 26, 2008 found out of 3,770

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package inserts in the database, 1,245 listed *starch* as an ingredient. Overall 65% of the medications with *starch* on the label did not specify the botanical source. Eight labels specified potato starch and three labels listed wheat as the source of the starch.

If the source of starch is not listed, the only way to determine the type of starch is to call the manufacturer. Although this seems like an easy task that will give the patient an immediate answer, it often turns out to be a frustrating process.

A common problem is that manufacturers do not always know what starch is used, largely because their raw materials are typically purchased from outside sources. Depending on the cost of certain starches, the type of starch could change routinely, making it difficult for manufacturers to know what ingredient they are using at any given time. In many cases it can take several hours or even days to get the right information from the company. Response can be further delayed if the call is placed after hours or on a holiday. This can pose a serious problem when the patient needs to start a potentially life-saving drug as soon as possible.

Another concern is cross-contamination of starches from different drugs. Even the slightest amount of gluten can cause symptoms in a patient with celiac disease. Just like cross-contamination can occur in a kitchen when preparing food, cross-contamination can occur within a pharmaceutical manufacturing facility when ingredients are prepared using the same equipment. For example, if a pill containing gluten is run on the same belt system as a pill without gluten, contamination has occurred and the medicine may no longer be safe for a patient with celiac to take.

THE SOLUTION

Labeling of inactive ingredients in medications can save lives. Three million Americans have celiac disease and another four million have allergies to inactive ingredients found in medication. Providing detailed information on the drug label will allow physicians and pharmacists to provide safe medications to their patients.

To achieve this goal, the National Foundation for Celiac Awareness (NFCA) is working closely with the American Society of Health-System Pharmacists

(ASHP) to educate pharmacists, physicians and the federal agencies about the issue. In April 2008, the NFCA and ASHP held a Gluten in Medications Educational Session and Stakeholders' Meeting to address the issues and discuss ways to move forward with labeling. Key members of the pharmaceutical community, government agencies, patient advocacy groups and pharmacists attended the meeting. Currently, NFCA and ASHP are working together to develop a citizens petition requesting labeling of all sources of starch on package inserts.

In addition, the ASHP approved a policy in June 2008 advocating that manufacturers declare the name and derivative source of all excipients in drug products on the official label.

In the meantime and in the absence of federal requirements for labeling inactive ingredients, the goal remains to educate health professionals about celiac disease and the exacerbating effects of gluten found not only in food but also in drugs. In addition, both NFCA and ASHP have plans to foster research on the influence of gluten in drug products in patients with celiac disease. ■

Resources

National Foundation for Celiac Awareness (NFCA)
www.celiaccentral.org

American Society of Health-System Pharmacists
www.celiaccentral.org

American Society of Health-System Pharmacists
www.ashp.org

National Institutes of Health
www.niddk.nih.gov

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