Gluten-Free Options for the Top 100 Pediatric Medications

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OBJECTIVE Celiac disease and gluten sensitivities are on the rise, with a greater prevalence of the condition in children than adults. Resources to ascertain gluten content exist but can be incomplete and focus on medications for adults. The objective of this research is to determine gluten-free status of the top 100 pediatric medications dispensed.

METHODS The top 100 pediatric medications were identified by using Optum Clinformatics Data Mart database. After list creation, manufacturers and National Drug Code (NDC) for each drug were procured and used to contact manufacturers directly for gluten content information.

RESULTS Evaluation of 689 NDCs was completed with 50.2% of medications documented to be gluten-free. Additional categories were confirmed gluten-free but cannot confirm cross-contamination (22.6%), cannot confirm gluten-free (25.7%), and contains gluten (1.5%). Resource tables were developed from findings though information may change, based on manufacturing ingredients and processing.

CONCLUSIONS Pediatric medications differ in gluten content, compared with medications for adults. Incomplete information exists regarding gluten content of medications, especially pediatric resources. Development of a pediatric-specific resource for gluten content of commonly dispensed medications in children and adolescents will hopefully benefit patients with celiac disease.

ABBREVIATIONS FDA, US Food and Drug Administration; HCl, hydrochloride; NDC, National Drug Code; penicillin VK, penicillin V potassium

KEYWORDS celiac disease; children; gluten; pediatric

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Introduction

Celiac disease is an immune-mediated condition characterized by inflammation of the small intestine from ingesting gluten, a protein found in wheat, barley, and rye.[1] Diagnosis of celiac disease and gluten sensitivity in the United States has increased in the past few decades with an average 7.5% increase per year, in addition to cases that have gone undiagnosed.[2] Children have a significantly greater prevalence of celiac disease than adults.[3] Currently, celiac disease has no cure, thus gluten avoidance not only in foods, but also in less commonly noted sources, such as medications, is the only treatment.[3] Previous research and analysis on the gluten status of medications have focused primarily on commonly dispensed adult medications.[4,5] Even with these data available, there is still a large unmet need of public resources for gluten status of medications and greater still among commonly dispensed medications for children. The purpose of this assessment is to summarize gluten-free status of the top 100 medications dispensed to children and adolescents by developing a pediatric-specific resource for health care professionals to use when prescribing medications for pediatric patients with gluten sensitivities.

Materials and Methods

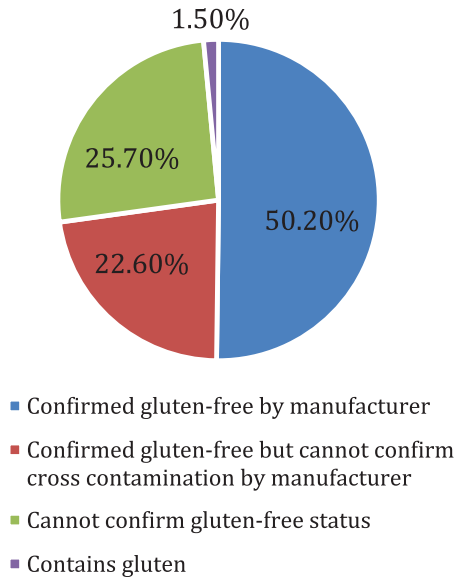
The top 100 dispensed medications to 10,000 patients younger than 18 years were identified from January 1, 2020, to December 31, 2020, using Optum Clinformatics.[6] Exclusion criteria consisted of non-oral medications and any National Drug Code (NDC) that was discontinued or no longer manufactured. Following the creation of the medication list, each drug was individually reviewed in the Lexicomp database[7] under Facts and Comparison's Product List to procure its NDC and manufacturer. Each drug manufacturer was subsequently contacted for gluten-free status, using the NDC/NDCs for all the top 100 medications. Manufacturers were first contacted through email, and if no response, investigators contacted companies via phone call(s). Information collected was organized by name, NDC, and gluten-free status. Gluten-free status was further differentiated into 4 categories: 1) confirmed gluten-free by manufacturer; 2) confirmed gluten-free but cannot

confirm cross-contamination by manufacturer, that is, ingredients were deemed gluten-free, but drug may have encountered gluten anytime during manufacturing process; 3) cannot confirm gluten-free status; and 4) contains gluten.

Results

A total of 689 NDCs was analyzed. The most dispensed medication was amoxicillin 400 mg/5 mL suspension with almost 2 million prescriptions dispensed, accounting for more than 7% of the total dispenses during the study period. Additional top 5 commonly dispensed medications were azithromycin 200 mg/5 mL suspension (4.6% of total prescription dispensed), cefdinir 250 mg/5 mL suspension (3.4%), prednisolone sodium phosphate 15 mg/5 mL solution (2.1%), and amoxicillin/potassium clavulanate 600 mg–42.9 mg/5 mL suspension (2%). Of the 689 NDCs reviewed, 346 (50.2%) were confirmed gluten-free by the manufacturer, 156 (22.6%) were confirmed gluten-free but could not confirm cross-contamination by the manufacturer, 177 (25.7%) could not confirm gluten-free status, and 10 (1.5%) contained gluten (Figure). Overall, 95 medications were identified to have at least 1 confirmed gluten-free option. Five medications were identified to not have a gluten-free option, which included clarithromycin 250 mg/5 mL suspension, levocetirizine dihydrochloride 2.5 mg/5 mL solution, mebendazole 100-mg chewable tablet, mefloquine hydrochloride (HCl) 250-mg tablet, and penicillin V potassium (VK) 250 mg/5 mL oral solution. Commonly used medications and their corresponding NDCs that were confirmed by the manufacturer to contain gluten included azithromycin 250 mg (59762-2198-XX), levocetirizine dihydrochloride 2.5 mg/5 mL solution (45802-0680-XX), lansoprazole 15-mg delayed-release capsule (00536-1236-XX, 00536-1324-XX), methylprednisolone 4-mg tablet (00603-4593-XX, 59746-0001-XX, 59762-4440-XX), prednisone 10-mg tablet (59746-0173-XX), and prednisone 20-mg tablet (59746-0175-XX). All NDCs for the following medications were confirmed gluten-free: acetaminophen-codeine 120 mg–12 mg/5 mL suspension, cefixime 100 mg/5 mL suspension, cefixime 200 mg/5 mL suspension, lisdexamfetamine of all strengths, prednisolone sodium phosphate 5 mg/5 mL and 25 mg/5 mL solution, and prednisolone sodium phosphate 15-mg disintegrating tablet. A resource table was developed to include all pediatric medications reviewed (Table).

Figure. Percentages of gluten content in the top 100 pediatric medications.



Discussion

Per the US Food and Drug Administration (FDA) requirement, for food products to be deemed "gluten-free" or "no gluten" on a label they must contain fewer than 20 parts per million of gluten.[8] However, the FDA only recommends that drug manufacturers use "contains no ingredient made from a gluten-containing grain (wheat, barley, or rye)" as a statement for medicines if true.[9] The statement if made is nonbinding and voluntary. If submitting a new drug application, manufacturers only need to ensure information is available to substantiate recommended labeling. If the drug application is already approved, manufacturers may add recommended labeling at any time if they can substantiate information but must add it to the next annual report. If using an alternative gluten statement or changing the product formulation to make a gluten statement, manufacturers must then submit a prior approval supplement. An example of alternative labeling (ie, "gluten-free") is not endorsed because the FDA has no established criteria for such statements on oral drug products. Furthermore, the FDA has not determined whether a gluten-free statement should refer to absence of intact gluten or should also require absence of gluten peptides.

Currently, the amount of gluten for a unit dose of an oral drug is estimated to be less than 0.5 mg, which is less gluten than in a gluten-free diet (ie, 5–50 mg).[9] Thus, the FDA infers that those patients who have positive response to a gluten-free diet should be at low risk for gluten-related gastrointestinal problems from the estimated gluten in an oral drug product. Patients with celiac disease should be advised to avoid oral medications labeled as containing wheat starch or flour; however, patients with gluten sensitivities may need additional information owing to unintentional intake of gluten from either drug excipients or the manufacturing process.[8,9]

Lack of gluten-free manufacturing policies is a barrier for patients with gluten sensitivities.[8] There are

currently no validated measures to detect or quantify gluten content in oral drug products.[9] Manufacturers may state their products are without gluten though they do not certify or test for gluten-free status.[5] Gluten categories for our pediatric resource were determined from manufacturers' responses in good faith, and cross-contamination was concluded to occur with an oral drug product if gluten may have been encountered at any time in the manufacturing process, though the ingredients were deemed gluten-free. Most patients with celiac disease can tolerate cross-contamination of approximately 10-mg gluten, but some sensitive patients may have an immune response to lower gluten content, leading them to attempt to eliminate or minimize exposure to gluten in drugs and other products.[8–10] Our findings identified 5 medications—clarithromycin 250 mg/5 mL suspension, levocetirizine dihydrochloride 2.5 mg/5 mL solution, mebendazole 100-mg chewable tablet, mefloquine HCl 250-mg tablet, and penicillin VK 250 mg/5 mL oral solution—that are without a gluten-free commonly used dosage form in the top 100 medications. If medications with gluten content are prescribed for patients with gluten sensitivities, the recommendation would be to identify an alternative dosage form (eg, penicillin VK solution to tablet), recommend a therapeutic alternative (eg, mefloquine tablet to doxycycline tablet),[5] or if no other alternative options exist, then the patient may proceed with caution given estimated gluten of 0.5 mg or less for a unit dose of oral drug.[9] Hopefully in the near future, patients will have additional alternatives, as several medications for celiac disease are in the drug development pipeline with therapeutic approaches consisting of breaking down gluten with enzymes, interrupting effects of gluten on the intestines, preventing gluten modification to reduce abnormal immune response, and interrupting the overall immune reaction from gluten.[11]

Limitations to our gluten-content medication list are the lack of over-the-counter drug products, as well as herbal and dietary supplements. Given the FDA ensures over-the-counter drug products for quality, effectiveness, and safety, similar recommendations for gluten-free status would carry through for their labeling. On the contrary, herbals and dietary supplements would not have the same oversight because they are not FDA approved, leaving their gluten content unknown or unsubstantiated.

Conclusion

Inactive ingredients produced from wheat starch or transferred through the manufacturing process can result in gluten content in medications.[4,12] A previous list of medications for adults found 18% of manufacturers specified their medications contain gluten.[4] Additionally, 69% indicated their medications were gluten-free, although only 17% tested their products and could provide documentation. Findings from our assessment differed, because 50% of medications were documented to be gluten-free, with only 1% confirmed as containing gluten. Currently, gluten information in package inserts is voluntary, as the FDA has issued guidance for manufacturers to voluntarily label medications if known to be gluten-free.[9] However, most medication package inserts have limited information regarding gluten, and potential sources of gluten are not always easily recognized by health care professionals.[8] Benefits from this collective pediatric-specific resource will hopefully improve patient care by providing pharmacists and other health care providers appropriate gluten-free prescription options for children with celiac disease and gluten sensitivities, though information should be updated periodically by contacting the manufacturer because gluten content may change.[8]

Article Information

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