February 2014

The Safety of Artificial Sweeteners and their Use in Pharmaceuticals

Kaila Bollinger  
Ohio Northern University

Maureen Moynihan  
Ohio Northern University

Adam Smith  
Ohio Northern University

Alison Steinbrunner  
Ohio Northern University

Karen Kier  
Ohio Northern University, k-kier@onu.edu

Follow this and additional works at: https://digitalcommons.onu.edu/paw_review

Part of the Pharmaceutics and Drug Design Commons, and the Preventive Medicine Commons

Recommended Citation


This Article is brought to you for free and open access by DigitalCommons@ONU. It has been accepted for inclusion in Pharmacy and Wellness Review by an authorized editor of DigitalCommons@ONU. For more information, please contact digitalcommons@onu.edu.
The Safety of Artificial Sweeteners and their Use in Pharmaceuticals

Kaila Bollinger, fifth-year pharmacy student from Bloomville, Ohio; Maureen Moynihan, fourth-year pharmacy student from Bloomfield Hills, Mich.; Adam Smith, fourth-year pharmacy student from Dublin, Ohio; Alison Steinbrunner, fifth-year pharmacy student from New Carlisle, Ohio; Karen Kier BSPh ’82, Ph.D., R.Ph., M.Sc., BCPS, BCACP, professor of clinical pharmacy and director of assessment, preventative care specialist, ONU HealthWise

Abstract
Artificial sweeteners are sugar substitutes that add sweetness to foods and beverages without the extra calories found in sugar. These additives are used to help patients with diabetes avoid hyperglycemia and assist people in losing weight or avoiding weight gain by providing a replacement to higher calorie sugar-sweetened foods. Artificial sweeteners can be found in many sugar-free beverages, candies and gum, as well as pharmaceutical products. Although artificial sweeteners are often recommended over the sugar-sweetened alternatives in weight loss and diabetes prevention, the use of such products is not without risk. Studies have been conducted to assess artificial sweeteners involvement in contributing to cancer, genotoxicity and diabetes. To provide optimal health care to patients, it is imperative to know the implications involved with these risks. Pharmaceutical products formulated for oral and peroral administration have been sweetened by both artificial and natural sweeteners, and the utilization of artificial sweeteners has been deemed more beneficial than its natural counterpart. As health care professionals, it is our job to counsel patients on the benefits of artificial sweeteners over natural sweeteners along with the importance of using artificial sweeteners in moderation.

Introduction and Background Information on Artificial Sweeteners
Currently there are five artificial sweeteners approved by the U.S. Food and Drug Administration (FDA) including sucralose, aspartame, saccharin, stevia and acesulfame potassium (acesulfame). These compounds are regulated by the FDA as food additives and were evaluated for safety before being made available for public consumption (Table 1). Artificial sweeteners are currently the gold standard as additives in food and beverages consumed by those with type II diabetes mellitus and those who either want to lose weight or avoid weight gain. Artificial sweeteners help diabetics avoid hyperglycemia and maintain a more consistent blood sugar level. Artificial sweeteners add little to no calories to achieve the equivalent sucrose sweetness within their food and beverage formulations, which makes artificial sweeteners a viable choice for those limiting their daily caloric intake. By limiting both sugar intake and overall calories consumed, the risk of developing diabetes and obesity decreases. However, artificial sweetener consumption has been linked to an increased cancer incidence, with both genotoxic and carcinogenic properties in studies conducted in lab rats. Subsequently, when more stringent safety studies were performed, an increase in cancer incidence was not observed in human subjects. However, long-term studies have not been conducted to assess the overall effect artificial sweeteners have in humans after consumption over a lifetime.

Toxicity Testing
A study done in 2002, at the Center of Advanced Study, Cell and Chromosome Research, Department of Botany at the University of Calcutta, in conjunction with the Department of Internal Medicine at the University of Kentucky, studied the genotoxicity of the artificial sweeteners aspartame, acesulfame and saccharin. Genotoxicity was evaluated according to how much damage was sustained to the DNA when exposed to external factors. The study population included mice that were fed increasing dosages of one sweetener, and their bone marrow tissue was analyzed for genotoxicity. From the test performed in this study it was concluded that each of the three sweeteners induced DNA damage in the mouse bone marrow cell. This study concluded that it is impossible to assess the long-term effects of artificial sweetener use, but use should be limited based on the genotoxic effects found within the study.

A bioassay evaluation of aspartame carcinogenicity in Sprague-Dawley rats was conducted by the Cesare Maltoni Cancer Research Center of the European Ramazzini Foundation. Aspartame was added to the rat’s normal feed at the concentrations of 100,000; 50,000; 10,000; 2,000; 400; 80 and from the control group 0 ppm. These concentrations were calibrated to parallel the human consumption of 5,000; 2,500; 500; 100; 20; 4 or 0 mg/kg, respectively, each day. Aspartame was added to the feed when the rats were 8 weeks old until natural death, upon which an extensive autopsy was conducted. Both the male and female population showed a significant increase in the incidence of malignant tumors with (p ≤ 0.05) for males and (p ≤ 0.01) as compared to controls. The study concluded that with aspartame consumption, the risk of malignant tumor development increased within the rat subjects. These findings show more research is necessary to adequately assess aspartame carcinogenicity with long-term consumption in the human population.

Sucrose versus Artificial Sweeteners
A prospective cohort study examined the association of artificially and sugar-sweetened beverages in the development of type II diabetes. The study included 51,529 men ages 40 to 75 years who were recruited to form a Health Professionals Follow-Up Study. The study consisted of questionnaires mailed every other year to assess health status and lifestyle factors. After excluding the men who did not respond to the survey and those with type II diabetes, cardiovascular disease and cancer, a 131-item semiquantitative food frequency...
The safety of artificial sweeteners and their use in pharmaceuticals

Preventive Medicine

Table 1. Overview of FDA Approved Artificial Sweeteners

<table>
<thead>
<tr>
<th>Artificial Sweetener</th>
<th>Brand Name</th>
<th>Sweetness Compared to Sugar</th>
<th>Physical Characteristics</th>
<th>Food Additive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sucralose</td>
<td>Splenda</td>
<td>600x</td>
<td>Heat-Stable</td>
<td>Diet Foods, Sugar-Free Beverages, Gum, Gelatin; can be used in baking</td>
</tr>
<tr>
<td>Aspartame</td>
<td>NutraSweet and Equal</td>
<td>220x</td>
<td>Combination of two amino acids</td>
<td>Sugar-Free Beverages</td>
</tr>
<tr>
<td>Saccharin</td>
<td>Sweet N'Low, Sweet Twin, NectaSweet</td>
<td>300x</td>
<td>Diet Foods and Beverages</td>
<td></td>
</tr>
<tr>
<td>Stevia</td>
<td>Truvia, Sun Crystals, Pure Via</td>
<td>200-300x</td>
<td>Dietary Supplement/Extracted from Stevia rebaudiana plant</td>
<td>Diet Foods and Beverages</td>
</tr>
<tr>
<td>Acesulfame</td>
<td>Sunett, Sweet One</td>
<td>200x</td>
<td>Heat-Stable</td>
<td>Mostly in Carbonated Beverages; Baking</td>
</tr>
</tbody>
</table>

A questionnaire was sent out to 40,389 qualified men every four years to assess the consumption of sugar-sweetened and artificially sweetened beverages. Artificially sweetened beverages included caffeinated, caffeine-free, and noncarbonated low-calorie colas. Sugar-sweetened beverages included caffeinated and caffeine-free colas; other carbonated sugar-sweetened beverages, and noncarbonated sugar-sweetened beverages (fruit punch, lemonade and other fruit drinks). Groups were divided into those that consumed sugar-sweetened beverages versus artificially sweetened beverages and then further divided into frequency of consumption.

A total of 2,680 incident cases of type II diabetes were noted over 20 years of follow-up. Hazard ratios (HR) were determined using a Cox proportional hazard to determine the association of sugar-sweetened versus artificially sweetened beverages to type II diabetes. Statistical adjustments were made for smoking, physical activity, alcohol intake, multivitamin use, family history of diabetes, high triglycerides, high blood pressure, diuretic use, previous weight change, low-calorie diet and body mass index (BMI). After adjustments were made, consumption of sugar-sweetened beverages was associated significantly to the development of type II diabetes with an HR of 1.24, confidence interval (CI) of (1.09 to 1.40) and a p-value <0.01. Consumption of artificially sweetened beverages did not show a significant association with type II diabetes (HR 1.09 [CI 0.98-1.21]) and p-value of 0.13, after adjustments.

The major limitation to the study was weak external validity (lack of generalizability) caused by the study population being solely comprised of adult, white males. Strengths included the measuring of beverage intake prior to type II diabetes development, similar socioeconomic status of the participants, beverage intake calculated as cumulative averages, a control present for several health and lifestyle factors and the large sample size. By measuring intake prior to the development of type II diabetes and adjusting for other health and lifestyle risk factors for type II diabetes, the study was able to limit many confounding variables that would likely have been a concern in determining the association of the two different sweeteners and type II diabetes. Although the study did not find significant statistical evidence for the association of artificial sweeteners to the development of type II diabetes, the study was limited to the effects of artificial sweeteners in adult, white males and cannot be properly generalized to include the general population. Therefore, the results were not conclusive in determining if artificial sweeteners have a reduced risk of type II diabetes when compared to natural sugars.

Pharmaceutical Application

Artificial sweeteners are extremely prevalent in the field of pharmaceutics. There is an abundance of oral medications that rely on this means of sweetening enhancement to produce a palatable dosage form for the patient. Dosage forms that rely on these sweetening enhancers include tablets, powders, solutions, suspensions, and medical products in these dosage forms range from prescription to nonprescription medications as well as herbs and vitamins.

Sweeteners such as sucrose have been used in the past to overcome the bitterness and odor of a large amount of medications for patients. An example would be the commonly prescribed pain management medication morphine sulfate IR in oral solution. Due to the chronic nature of this medication; sucrose in this solution can prove to be problematic. Two
issues predominate with this usage: dental caries and hyperglycemia in diabetic patients. Despite these issues, patient adherence to the medication still dictates the use of these sweeteners. Recently, artificial sweeteners have been a preferred alternative to classic sweeteners to alleviate the dental erosion and large intake of sugars. Studies such as Koning et al. and Nettleton et al. show conflicting data with the latter claiming that artificial sweeteners are related to the diagnosis of type II diabetes.8,11 With inconclusive data health care providers, and specifically pharmacists, can play a large role in counseling patients and selecting safer medications that are artificially sweetened.

A population that is greatly influenced by sweeteners is pediatrics. In pharmacy, sweeteners are used extensively in regard to ease of administration of medication to children. Children are especially susceptible to dental caries and tooth erosion from an excess of sweetener in their diet as well as medications. As more pediatric medications come on the market, sweeteners will become a more problematic issue. Medications such as Chlor-Trimeton contain sucrose in the syrup formulation while other drugs such as Children’s Tyle-nol elixir contains both aspartame and mannitol: a sugar and an artificial sweetener. Brief, short-term use has not proven to cause such adverse effects; however, long-term use of sucrose-sweetened medications has been associated with dental caries, tooth erosion, and diabetes.12 Therefore, short-term use is a way in which artificial sweeteners can provide less adverse effects and be a better sweetener in pediatric medications.

Pharmacists can provide education to patients on artificial sweeteners through medication therapy management. Making the patient aware of sweetening agents, whether it is sucrose or an artificial sweetener, can improve the patient’s conditions as well as his or her quality of life. It is important as pharmacists to explain how neither natural nor artificial sweeteners are healthy, yet artificial sweeteners are the preferred choice of the two.1 This is especially imperative in patients who have conditions such as high blood pressure, obesity and diabetes.

Conclusion
Sweetener enhancers are heavily used throughout society whether it is through diet or pharmaceutical products. With diets high in sugars, prevalence of type II diabetes and obesity have reached record-breaking highs. Through extensive research, we have evaluated and compared the effects of using sugar sweeteners such as sucrose versus FDA-approved artificial sweeteners. Through the studies conducted, we can conclude that the adverse effects of sugar sweeteners are proven to be more detrimental than those of artificial sweeteners. Despite studies claiming that artificial sweeteners may have negative health effects, the data is inconclusive and the diagnoses of diabetes and obesity were attributed more towards sugar sweeteners than artificial sweeteners.

To maintain patient adherence; therefore, the benefits of artificial sweeteners outweigh the risks. With artificial sweeteners, moderation is essential. Patients cannot avoid the intake of these sweeteners in their medications; however, dietary adjustments should be recommended to reduce the intake of artificial sweeteners. By educating patients, pharmacists can play a major role in helping patients to more safely consume products with artificial sweeteners.

References