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Unexpected Toxicity From Drug Products - A Blog Post from IVT Network

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INTRODUCTION

A recent news story describing loss of life caused by excessive consumption of licorice candy has been widely reported (1-3). This story involved a highly unlikely and unexpected cause of death – eating candy! This event is a reminder of several similar pharmaceutical occurrences -- serious unexpected consequences involving the content of drug products. No contamination, impurity, or other product adulteration is involved in the topics described. Persons who have suffered these toxic occurrences were innocent victims; their consequences could have been prevented if they had known more about products they were consuming.

Glycyrrhizin in Licorice

A September 2020 incident involved the death of a 54-year old Massachusetts construction worker who consumed a large amount of natural black licorice candy. Natural licorice contains glycyrrhizin, an ingredient with significant pharmacological activity. This ingredient and its effects were obviously unknown to the deceased individual. Ironically, the victim had been previously consuming red licorice -- not containing toxic glycyrrhizin -- but switched to eating natural black licorice that ultimately caused his death. FDA has stated that eating as little as 2 ounces of natural black licorice every day for two weeks could cause a heart rhythm problem due to an imbalance of sodium and potassium electrolytes (4). FDA has also published maximum allowable levels of glycyrrhizin in foods (5). The deceased victim consumed more than 1 pound of black licorice every day for several weeks prior to death. Testing indicated dangerously low potassium levels when he was admitted to the hospital.

Metabolized glycyrrhizin is well known to interfere with a specific biochemical mechanism in which cortisol levels are increased. Increased cortisol causes sodium retention and decreases potassium (hypokalemia); sodium and potassium electrolyte imbalance affects muscle contraction including cardiac muscle contraction. This event and the pharmacologic effects are is more completely described in a YouTube video (6).

Non-Toxic Licorice Products and Deglycyrrhizinated Licorice (DGL). Most commercially available licorice candy in the United States is not toxic. The subject event involved natural black licorice products containing glycyrrhizin. Other black licorice products are not truly licorice; they are sweetened mixtures flavored with anise or other flavoring, but are labeled "black licorice." These "black licorice" do not contain glycyrrhizin and do not cause glycyrrhizin pharmacologic effects. Similar "red licorice" products containing strawberry, raspberry, or other flavors also do not cause glycyrrhizin pharmacologic effects. DGL licorice products in which glycyrrhizin is removed from the natural product are commercially available. Patients consuming licorice for various herbal therapy use DGL licorice to minimize potential natural licorice toxic effects (7).

Discussion Topics.

This discussion describes occurrences with potentially serious outcomes caused by pharmaceutical products. Its objective is to remind readers of the importance of knowing about medications being consumed. Events described are common occurrences. Example events with different causes are discussed. Events described involve readily available over-the-counter (OTC) products as well as Rx products. Topics discussed are as follows:

- Pharmaceutical "candy" dosage forms
- Acetaminophen and combination products
- Dietary supplement (herbal) drug interactions.

PHARMACEUTICAL "CANDY" DOSAGE FORMS

Numerous pharmaceutical dosage forms resembling candy products are now commercially available. These include gummies, chewable tablets, soft chewables, chocolates, brownies, and other confectionary products. Drugs in these formulations include multivitamins, individual vitamins, herbal products, melatonin, iron, fiber, cranberry, CBD products, laxatives, apple cider vinegar, and many others. These formulations are useful for individuals who have difficulty swallowing tablets and capsules; they also help mask bitter-tasting drugs, facilitate administration to children, and have other beneficial applications. Chewy formulations are also useful for administering drugs to small domestic animals – chewable meat-flavored formulations are very useful for dogs.

The formulations of these products are excellent in appearance and taste, and are commercially successful. However, they also must be treated by users as serious medical products. The appearance and taste of these products present an increased potential for overdose, especially in children who may not understand differences between medication and candy.

Gummy vitamins are especially troubling products. There are numerous reports of gummy vitamin overdose on the internet – even by adults who like the product taste. Gummy vitamins and other gummy medications in the home must be stored in secure locations separate from candy and food; they must not be accessible by children. Toxicity from vitamin overdose is due to fat-soluble vitamins (Vitamins A, D, E, K); these vitamins are stored in the liver and are not readily excreted. See YouTube video (8) for an example of excessive gummy vitamin consumption and toxic effects on the liver and on bones.

The commercial availability of other drugs in gummy and other "candy" formulations is likely to cause similar overdose events. Chocolate-flavored laxative overdosage has long been a problem, either by inadvertent administration or as a juvenile prank. See YouTube video for detailed explanation of effects from consuming excessive candy laxative products (9). Candy formulations of pharmaceutical products fulfill a definite therapeutic need – but also are a definite risk.

ACETAMINOPHEN PRODUCTS

Acetaminophen is a generic drug with analgesic and antipyretic (fever-reducing) properties. Its chemical name is N-acetyl para-aminophenol, or APAP. It is also known as paracetamol in Europe and many countries. Its USA proprietary name is Tylenol. Toxicity from APAP overdose has been a significant problem for many years. 2017 Poison Control Center data indicate ~70,000 individual exposures involving APAP alone and ~40,000 incidents of APAP in combination with other drugs. APAP accounts for 82,000 ED visits annually, APAP is the most common cause of acute liver failure, and the primary reason for emergency liver transplantation (10).

APAP toxicity occurs because the therapeutic dose is very close to the toxic dose, i.e., APAP has a narrow therapeutic index. The maximum daily recommended APAP dose for adults is 2000 mg. The APAP metabolite may cause liver damage when the dosage is too high and when dosage has occurred over an extended time period. Liver toxicity is also more likely when combined with alcohol, and when patients have pre-existing liver damage such as from hepatitis or cirrhosis.

Why Overdosage?

Patients consume a toxic APAP dose for several reasons. Some do not read or understand the directions on the product label. Another is that they may deliberately administer an increased dosage vs. labeled directions because they feel they need additional drug for efficacy; post-surgical patients may overdose on opioids for pain relief without realizing the potential for APAP overdose. Patients taking multiple products containing APAP as part of a commercial products is another cause; the combined APAP dosage from all products may be toxic.

Products Containing APAP. There are numerous commercial products containing APAP. Products containing APAP alone are available in various amounts. For example,

- Tylenol Tablets contain APAP 325 mg
- Tylenol Extra-Strength Tablets contain APAP 500 mg
- Tylenol 8 hour Tablets for arthritis contains APAP 650 mg

There are also numerous products containing APAP with other drugs in OTC and Rx products.

OTC Products

- Theraflu Syrup. APAP 650 mg, dextromethorphan and phenylephrine / 30 mL
- Walgreens Sinus Pressure & Pain. APAP 325 mg, guiaphenesin, phenylephrine
- Dristan Cold. APAP 162.5 mg, chlorpheniramine, phenylephrine
- Contac Cold and Flu. APAP 500 mg, chlorpheniramine, phenylephrine
- Tylenol PM contains APAP 500 mg, diphenhydramine
- Alka-Setzer Plus Sinus & Cold. APAP 325 mg, dextromethorphan, phenylephrine
- ZzzQuil Night Pain. APAP 1000 mg, diphenhydramine

Rx Products

Note FDA maximum APAP dose is 325 mg/tablet.

- Tylenol with codeine. APAP 325 mg, codeine
- Norco. APAP 325 mg, hydrocodone
- Percocet. APAP 325 mg, oxycodone
- Vicodin. APAP 325 mg, oxycodone

Listings of additional drug products containing APAP are referenced (11).

Acetaminophen Toxicity from Consuming Multiple Products. APAP toxicity may occur when multiple products are consumed without consideration for the combined APAP dosage. For example, a flu patient may take several doses each of Tylenol Extra Strength and Contac Cold & Flu during the day and ZzzQuil at bedtime – a total APAP dose far exceeding 3000 mg APAP, the maximum recommended daily APAP dose. The patient followed the recommended dosage directions on each package; these directions are for each product taken individually without regard to other medications. The total combined APAP dosage from all products must be considered.

FDA Publications. FDA has published numerous notifications addressing safe use of APAP (12). Indiscriminate or careless dosage of APAP is a definite problem.

DIETARY SUPPLEMENTS (HERBALS) DRUG INTERACTIONS

Dietary supplements (aka herbal products) are widely consumed in the global marketplace (13). Treatment of certain physical conditions as well as positive effects, e.g., mental alertness, have been attributed to herbal products. Herbal products are not perceived to be drugs. Patients incorrectly assume that since herbals are “natural” and are often located in the vitamin aisle of

the supermarket, they must not be drugs – an incorrect assumption.

Herbal products may have pharmacological effects and may also interact with prescribed drugs being taken. FDA identified specific drug interactions with dietary supplements many years ago. (14,15). For example, St. John's Wort is known to reduce blood levels of digoxin, lovastatin, and sildenafil due to its effect on liver enzymes. Many widely used herbals such as garlic, gingko, and ginseng affect the blood clotting mechanism. Patients who are taking anticoagulant therapy(Coumadin, Pradaxa, Xarelto, Eliquis, others) as part of cardiac or other treatment may experience prolonged bleeding due to the effects of herbals (16). Excessive bleeding during minor surgeries or dental procedures may require termination of the procedure. One manager commented that a family member developed a nosebleed (epistaxis) while at a family party at a public restaurant; 911 was called and paramedics attempted treatment. Bleeding could not be stopped and the patient was hospitalized. The patient was currently taking Coumadin (warfarin); the paramedic commented "This happens all the time."

There are numerous references describing herbal products and potential drug interactions (17,18). FDA does not approve dietary supplements, although FDA does inspect manufacturing facilities for these products. FDA has requested that patients report problems with dietary supplements (19).

Patients must tell their physicians that they are taking dietary supplements to ensure that their effects are considered along with other prescribed medications.

SUMMARY AND FINAL THOUGHTS

This discussion has addressed unexpected and potentially serious problems with pharmaceutical products caused by inadvertent and improper use. Victims in many of these cases probably believe they were correctly taking drug products, but their dosing resulted in toxic effects.

"Candy" formulations of drug products may be overdosed due to their good taste. Patients forget the seriousness of the medications and suffer consequential effects; children especially may be unknowing victims. APAP overdose may have occurred due to its APAP inclusion in multiple products being concomitantly consumed – another innocent dosing error with very serious consequences. The number of poison center and ED visits are testament to the severity of APAP problem; liver transplants are also caused by APAP overdose. Prescribed drugs may interact with dietary supplements causing increased or decreased therapeutic effects.

Each of the above are preventable if patients proactively learn about the drugs they consume. Information is readily available through searches on the internet. Communication with pharmacists and other healthcare professionals is another source of information. Easy availability of OTC products, "candy" formulations, and "natural" herbal products must not cause diminished attention to the selection and administration of drugs – taking drugs is serious and truly may be life-threatening.

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