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Rebecca Airel
Ohio Northern University

Kayla Durkin
Ohio Northern University

Taylor Gauthier
Ohio Northern University

Jamie Amero
Ohio Northern University

Natalie A. DiPietro
Ohio Northern University, n-dipietro@onu.edu

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An Update on Acetaminophen Labeling Changes: A Pharmacist's Call to Action

Rebecca Airel, fourth-year pharmacy student from Strongsville, Ohio; Kayla Durkin, fourth-year pharmacy student from Valencia, Pa.; Taylor Gauthier, fifth-year pharmacy student from Winnebago, Ill.; Jamie Amero, fifth-year pharmacy student from Boardman, Ohio; **Natalie A. DiPietro**, PharmD '01, MPH, assistant professor of pharmacy practice

Abstract

Due to the number of acetaminophen overdoses each year, the Food and Drug Administration and the National Center for Prescription Drug Programs made changes and recommendations regarding the labeling of acetaminophen-containing products. It is important for pharmacists to understand these changes and to educate patients on the correct use of these products.

Introduction

Acetaminophen is one of the most commonly used medications in the United States. A 2006 survey showed that during any given week, 19 percent of adults and 11 percent of children were using acetaminophen-containing products.¹ If taken in excess, acetaminophen can cause liver injury. The Food and Drug Administration (FDA) estimates that 14 to 21 percent of all acetaminophen overdoses are not intended; however, some patients may intentionally overdose on acetaminophen.² Since the 1990s, efforts have been made to decrease the number of acetaminophen-related liver injuries, but medical literature continues to show that acetaminophen-related liver injuries are still a serious public health problem.³ Recently the FDA and the National Center for Prescription Drug Programs (NCPDP) have taken actions to help mitigate this problem. Labeling of prescription products containing acetaminophen will be changing, and suggestions for the labeling of over the counter (OTC) products were proposed as well. With the new labeling changes to come out within the next few years, pharmacists can help play a role in overdose prevention by providing patient counseling and education.

Background

In the years 1998-2003, acetaminophen-related liver injury was the leading cause of acute liver failure in the United States.⁴ Acetaminophen does not harm the liver directly; instead the harm is caused by one of its metabolites.⁵ A small percentage of acetaminophen is excreted unchanged in the urine, but the remaining amount is metabolized in the liver. In adults, approximately 75 percent of acetaminophen is broken down by the liver into inactive metabolites. The rest is metabolized by CYP2E1 to form N-acetyl-parabenzquinoneimine (NAPQI). Normally the body rids itself of NAPQI by binding it with glutathione and excreting it. During an overdose, the production of NAPQI exceeds the supply of glutathione causing a toxic buildup of NAPQI. Patients with a history of chronic alcohol use, binge drinking, or liver disease may be more prone to liver injury from acetaminophen because of increased production of toxic metabolites or decreased clearance of the metabolites.^{3,6}

Symptoms of acetaminophen overdose vary.⁵ Some patients appear asymptomatic while others experience GI symptoms or pain in the upper right quadrant. Initial signs of hepatic failure such as metabolic acidosis start to occur within 24 to 72 hours of overdose.

Acetaminophen overdose is diagnosed by patient history and current acetaminophen levels.⁶ The antidote of choice is N-acetylcysteine.⁵ N-acetylcysteine is most effective when administered no more than 8-10 hours after ingestion of acetaminophen, but may be effective if started within 24 hours.^{5,6} Treatment is continued until either the patient shows clinical and laboratory improvement, the patient receives a liver transplant, or death occurs. Mortality associated with acetaminophen-related acute liver failure is nearly 30 percent and is often due to cerebral edema. If the patient survives, the liver will typically return to baseline function within three months.⁶

Prescription Label Changes

On January 13, 2011, the FDA released information regarding changes of acetaminophen in prescription combination products. The main focus of the changes included limiting the amount of acetaminophen to no more than 325 mg in each tablet or capsule.⁷ Many acetaminophen overdoses are unintentional and are due to the patient's lack of knowledge about products containing acetaminophen. The FDA hopes to prevent these unintentional overdoses by limiting the amount of acetaminophen in prescription products.³ Furthermore, the FDA also requires an update on the labels of prescription combination acetaminophen products.⁷ Manufacturers will need to include a boxed warning on the label about the potential risk for severe liver injury and a warning regarding the potential for allergic reactions.⁸ There will be a three-year period for all manufacturers to re-formulate their products to adhere to these new regulations, with a deadline in 2014. For a list of prescription drugs that are affected, refer to the following website: <http://www.fda.gov/Drugs/DrugSafety/ucm239821.htm>.⁹

The NCPDP developed a work group to help form standard best practices and suggestions for prescription labels of products containing acetaminophen. The NCPDP work group developed recommendations to improve labels by creating similarities between OTC and prescription labels. Their goal is to decrease patient misinterpretation of the label, which may reduce the occurrence of acetaminophen overdose. Table 1 shows recommendations made by NCPDP.¹⁰

OTC Label Changes

At the time of this writing, the FDA's decision did not affect OTC products, although in May 2011 the FDA Advisory Panel for Nonprescription Medications released recommendations for OTC medications (Table 2).

OTC products containing acetaminophen are not officially affected by the FDA's decision, but McNeil Consumer Healthcare (the manufacturer of Tylenol®) announced changes to their products in response to the new recommendations that are expected to occur in 2012. A new maximum daily dose will be provided for regular strength and extra strength formulations. McNeil Consumer Healthcare also plans on changing their liquid formulations to make one consistent liquid dose for both children's and infant's Tylenol®. Furthermore, dosing instructions will be based on age and weight and will be provided for children as young as six months of age. The manufacturer hopes these changes will help eliminate medication errors and decrease the chance of accidental acetaminophen overdoses.¹¹

The NCPDP suggests that OTC labeling should change as well to help patients avoid acetaminophen overdoses. Suggested label changes include highlighting "acetaminophen" under the active ingredients portion and adding more caution elements to the warning section.¹⁰

Pharmacist Involvement

As members of the FDA met to discuss acetaminophen, they focused on a quote from Paracelsus, "Everything is a poison. What differentiates a poison from a remedy is the dose."¹² This quote stresses the importance of the pharmacist's role in educating patients and caregivers about proper dosing and use of acetaminophen-containing products (Tables 3 and 4). A government study found that almost 89 million American adults of various age, race, and economic status suffer from low health literacy, which refers to ability to make health decisions and follow treatment instructions. Given the large number of individuals with low health literacy, it is important for pharmacists to appropriately counsel all patients and caregivers. This would help minimize the likelihood of negative outcomes such as more serious medical problems, increased medical costs, and more doctor and hospital visits.¹³

Table 1. NCPDP Recommendations for Prescription Labeling¹⁰

- Complete spelling of active ingredients in acetaminophen-containing drugs (avoid use of the abbreviation "APAP")
- Standard acetaminophen use and liver damage warning label
- Prioritize the warning label on packaging
- Acetaminophen warning icon on product to ensure patient awareness
- Use plain language principles and patient-centered labels to increase patient comprehension

Table 2. Suggestions made by the FDA Advisory Panel for Nonprescription Medications¹¹

- One strength of liquid, chewable, and tablet form (currently there are 7 different strengths)
- Children's dosing instruction begin at 6 months
- Dosing based on weight, not just age
- Dosing device standards on spoons and cups with a consistent unit for measuring (current units include mL, cc, and tsp)

Table 3. Counseling Points For Adult Patients Using Acetaminophen-containing Products¹⁵

- Do not exceed 4 grams/day
- Do not take multiple acetaminophen-containing products
- Do not drink alcohol while taking acetaminophen-containing products
- Use has caused severe liver injury and cases of hypersensitivity reactions
- Report anytime more was taken than directed
- Report adverse events

Table 4. Counseling Points for Advising Parents or Other Caregivers on Acetaminophen Use in Children

- Do not give multiple medications containing acetaminophen.¹⁶
- Give only as long as necessary; check with the health care provider if the child needs medication for more than a few days.¹⁶
- Since labels are at an 8th grade reading ability (and almost half of American adults read below this level), explain the label and how to calculate and measure doses.¹⁷
 - Explain:
 - appropriate use of measuring devices
 - how to measure correct amount
 - dosing schedule¹⁶
- Contact doctor if the infant or child is lethargic or difficult to wake up.¹⁶
- Use weight-based dosing; not to exceed 5 doses per day.¹⁷
- There are different concentrations in various preparations.¹⁷
 - Given the anticipated changes to the OTC products, always confirm the formulation of the product being used; do not assume the caregiver has the most current product.⁸
- Use a single liquid preparation for all infants and children in a household.¹⁷
- Fevers are protective mechanisms and do not always need treated.¹⁷

A study surveying patients' knowledge related to acetaminophen recognition, dosing, and toxicity showed the need for proper counseling by a healthcare provider. Patients (n=284) 19 years or older were questioned about current and/or recent use of pain, cold, or allergy medications. Out of patients reporting use, only 25 percent knew the active ingredient. Less than half of the patients knew that Tylenol® and acetaminophen were synonymous and even fewer knew that APAP was also an alternative name. Only 13 percent of patients correctly identified three labels as containing Tylenol®. Although the majority of patients knew the potential harm of Tylenol®, some thought taking a harmful amount was difficult or impossible. Few patients knew the correct dose and many patients chose doses at toxic levels.¹⁴ This study showed that without appropriate knowledge on terminology, toxicity, and dosing of acetaminophen, the potential for harm exists. Counseling and patient education, along with the recently announced changes to strength and labeling of products, are key to reducing the incidence of acetaminophen overdose.

Multiple studies have shown that acetaminophen overdose affects children as well. Children do not reach adult levels of hepatic metabolism and excretion until they are about 12 years old.¹⁶ There have been a few reports of toxicity at doses of 50-75 mg/kg/day.¹⁶

Studies have found that overdoses occurred when teaspoonful quantities of infant drops were given instead of the children's liquid formulation and when regular strength tablets were given instead of children's chewable tablets.¹⁷ In addition, another study was performed to assess the impact of dosing instruments and parents' ability to correctly use them. It was observed that parents (n=302) were more likely to make dosing errors when using a dosing cup compared to other dosing forms due to confusion of teaspoon versus tablespoon instructions, assumptions that the full cup indicated the unit dose, and lack of eye-level dose verifications.¹⁸ Data has shown that there are high rates of errors in dosing infant acetaminophen, even among parents with adequate health literacy; a pictogram may be beneficial to educate patients on proper dosing.¹⁹

For these reasons, caregivers should be informed about proper dosing and accurate use of dosing instruments.¹⁸ Parents may consult the pediatrician if the child seems nauseated, vomits, and/or becomes lethargic after consuming these products. However, by that time, liver injury may have already occurred.¹⁷ Therefore, it is important for caregivers to know the instructions for dosing and signs of potential toxicity.

Medicines in My Home (MIMH) is an interactive program created by the FDA to teach consumers how to properly choose and use OTC medications. Pharmacists can utilize these resources or refer their patients to the website: <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/ucm092139.htm>.

Conclusion

Based on the information known about acetaminophen associated hepatotoxicity due to overdose and the FDA's recent actions regarding acetaminophen labeling, pharmacists should educate patients and caregivers on these changes and counsel them on proper use and dosing of acetaminophen-containing products.

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