

Medicare Part D Drug News Update Acetaminophen (APAP) Overuse: Risks, Developments, and Recommendations

Introduction

Acetaminophen (APAP) is a common household drug used for its analgesic and antipyretic properties. Recent evidence and discussions, however, have illuminated the myriad hazards and contributing factors associated with APAP overuse of both prescription and over-the-counter (OTC) products. Whether intentional or unintentional, APAP consumed in excess of 4 grams per day is associated with increased morbidity and mortality.

A known hepatotoxin, APAP is the most common cause of acute liver failure (ALF) in the United States; in fact, over 50% of all ALF cases are a direct result of APAP overuse.¹ Despite this knowledge, the incidence of hepatotoxicity is on the rise. One group reported that cases of ALF attributed to acetaminophen overuse increased from 28% in 1998 to 52% in 2004.² Risk factors for APAP-attributed hepatotoxicity include: the concomitant use of multiple APAP-containing products, age greater than 40 years, concomitant drug use (e.g. anticonvulsants such as phenobarbital, isoniazid, and warfarin, etc.), chronic alcohol ingestion (i.e. three or more drinks per day), and serious liver conditions such as acute viral hepatitis.³

APAP overuse has also been linked to renal failure, although the mechanisms are less clear. One study reported that a maximum daily dosage of more than 4 grams per day increased the risk of kidney damage by approximately 4 times compared to nonusers.⁴ Other toxicities associated with APAP use include serious skin reactions such as Stevens - Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP), which can occur with first-time use or at any point during which APAP is being taken. On August 1, 2013, the FDA issued an announcement informing the public of these rare but serious skin reactions.

APAP Overuse

The concomitant use of multiple APAP-containing products is the primary cause of unintentional overuse. Reports indicate that 38% of patients with unintentional overdose of APAP were taking two different preparations simultaneously.⁵ Many of the top selling prescription combination analgesics, such as Vicodin[®] (APAP and hydrocodone) and Percocet[®] (APAP and oxycodone), contain APAP. Compounding the problem is the fact that APAP can be found in many OTC cold, allergy, pain, and sleep medications as well, which for the unsuspecting consumer, can lead to therapeutic redundancy and unintentional overuse.

Also, APAP overuse due to overprescribing continues to be a widespread problem. It is of paramount importance that the mindful clinician continues to limit the maximum daily dose of APAP to no more than 4 grams per day when prescribing and recommending APAP-containing products. Adherence to the FDA-approved maximum daily dose of APAP not only prevents potential toxicities, but may also alleviate significant legal risk in the event of an APAP-related adverse event.

Regulatory Developments

Regulatory developments and partnerships have been implemented in order to combat overprescribing. The Centers for Medicare and Medicaid Services (CMS) has established the Overutilization Monitoring System (OMS), a program that assists Part D sponsors in preventing the over-dispensing of prescription medications, including those containing APAP. CMS provides Part D sponsors with reports that identify beneficiaries with potential overutilization issues. In turn, Part D sponsors are required to investigate identified overutilization issues and outreach with prescribers regarding daily doses of APAP exceeding 4 grams. Plan sponsors are also working with network pharmacies through adjudication software, pharmacy education, etc., to perform pharmaceutical care to prevent inappropriate dispensing.

In January 2011, the FDA issued a regulation regarding prescription combination products which limits the maximum amount of APAP in each tablet to 325 milligrams, in hopes of mitigating the overuse potential of APAP. The deadline for manufacturers to comply was January 2014. New labeling requirements have been implemented as well: all prescription drug products containing APAP must now include a black box warning regarding liver injury and the risk of serious skin reactions.

Recommendations

APAP overuse is a threat to patient safety. The concomitant use of APAP-containing products and overprescribing are contributing factors to overuse. Healthcare professionals have formed valuable partnerships in order to combat this issue. Additionally, you, as a clinician invested in optimal outcomes, can put into practice the following recommendations:

1. Consider the long-term safety and efficacy of treatment when recommending or prescribing an APAP-containing medication.
2. Assess patients for risk factors associated with APAP-attributed hepatotoxicity.
3. Ask patients about all OTC products they are currently taking and confirm that the potential maximum daily amount of APAP, in conjunction with prescription medications, does not exceed 4 grams.
4. Consider limiting treatment to the use of a sole APAP-containing medication.
5. Review other options when managing acute and chronic pain, such as NSAIDs and APAP-free opioids.
6. Advise patients to read the labels of OTC products to avoid taking multiple APAP-containing products.
7. Inform patients of the signs and symptoms of adverse effects and toxicities associated with APAP overuse.
8. Consult and direct patients to the Acetaminophen Awareness Coalition website for a list of APAP-containing products: <http://www.knowyourdose.org>
9. Report all adverse events to the FDA MedWatch program: <http://www.fda.gov/Safety/MedWatch>

This information is not intended to replace your clinical judgment. Only you, in direct consultation with your patient, may determine if drug therapy benefits outweigh the potential risk. If a change is warranted, please advise your patient directly.

References

1. Ostapowicz G, Fontana RJ, Schiødt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med.* 2002;137(12):947-54.
2. Lee WM. Acetaminophen toxicity: changing perceptions on a social/medical issue. *Hepatology.* 2007;46(4):966-70.
3. Chun LJ, Tong MJ, Busuttill RW, Hiatt JR. Acetaminophen hepatotoxicity and acute liver failure. *J Clin Gastroenterol.* 2009;43(4):342-9.
4. Kelkar M, Cleves MA, Foster HR, Hogan WR, James LP, Martin BC. Acute and chronic acetaminophen use and renal disease: a case-control study using pharmacy and medical claims. *J Manag Care Pharm.* 2012;18(3):234-46.
5. Larson AM, Polson J, Fontana RJ, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology.* 2005;42(6):1364-72.
6. FDA Drug Safety Communication: Prescription Acetaminophen Products to be Limited to 325 mg Per Dosage Unit; Boxed Warning Will Highlight Potential for Severe Liver Failure. January 13, 2011. Available at: <http://www.fda.gov/drugs/drugsafety/ucm239821.htm>. Accessed November 21, 2013.