Safe Use of Acetaminophen-containing Combination Products

On January 15, 2014 the Illinois Drug Utilization Review Board evaluated acetaminophen use. Consumers in the United States increasingly use acetaminophen-containing over-the-counter (OTC) products and prescription narcotic combination products. Over 88,500 Illinois Medicaid clients filled at least 12 million prescriptions for combination products containing more than 325 mg of acetaminophen per dosage unit in 2013.

Acetaminophen-induced toxicity. There is little difference between the maximum 4 gram daily dose and a harmful dose of acetaminophen. Higher doses elevate liver enzymes resulting in acute hepatic failure. Hepatic failure may require liver transplantation and may also result in death. Concurrent hepatic disease and alcohol use facilitate toxic effects at lower acetaminophen doses. Acetaminophen use is the leading cause of acute liver failure in the United States. Acetaminophen overdose led to over 56,000 Emergency Room visits, 26,000 hospitalizations, and 458 deaths in the 1990's. At least 84% of the cases of liver injury in pediatric patients have been due to acetaminophen medication dosing errors. Analysis of acetaminophen-induced hepatic injury and fatalities identified concurrent use of multiple acetaminophen-containing products and doses greater than 500 mg of acetaminophen as primarily causing hepatic injury.[1-3]

FDA actions. The Food and Drug Administration (FDA) has tried to improve safe acetaminophen use since the 1990's. Public advisory meetings and education campaigns targeted safe use of acetaminophen and non-steroidal anti-inflammatory drugs. Changes to prescription labeling to avoid the acetaminophen abbreviation "APAP" and warnings about use of multiple acetaminophen-containing products concurrently were issued. Labeling changes for OTC products have warned about liver injury, use of multiple acetaminophen-containing products, and the contributing role of alcohol in acetaminophen-induced hepatic injury. In 2011 weight-based dosing for children 2-12 years old was instituted in addition to age-based dosing, a 10-15 mg/kg dose was recommended for infants 6 months to 2 years of age, and an infant liquid dosage concentration of 160 mg/5 mL became available.[1-3]

In 2011 the FDA also requested manufacturers to no longer make oral prescription products containing acetaminophen doses > 325 mg per dosage unit. This requirement, effective January 1, 2014, continues efforts to decrease acetaminophen-induced toxicity.[2] In January 2014, the FDA launched a public provider education campaign asking prescribers not to write prescriptions for products that contain more than 325 mg of acetaminophen per dosage unit and pharmacists to no longer dispense these products. Dosing directions can still be 1-2 tabs, so the patient can get more than 325 mg for a dose if needed.[4]

Illinois Department of Health and Human Services. The Bureau of Pharmacy Services made all prescription oral dosage forms that contain > 325 mg acetaminophen per dosage unit *Non-Preferred* effective April 1, 2014. The 225 products are primarily acetaminophen-containing narcotic combination products and a few combination products for treating migraines, coughs, and colds. Many of these products already required Prior Authorization. To further facilitate safe acetaminophen use the Bureau of Pharmacy Services and the Illinois Drug Utilization Review Board have reviewed and adjusted age limits and maximum quantities for all acetaminophen-containing prescription products.

Providers are asked to choose preferred products that contain a maximum of 325 mg of acetaminophen per dosage unit. Availability of products containing more than 325 mg of acetaminophen should be decreasing as manufacturers reformulate or remove their products from the market.

Dosing of acetaminophen and narcotic combination products. Particular care is advised in dosing acetaminophen and narcotic combination products in the pediatric population. Opioid dependence can occur in children if products are used for 5-7 days. The American Academy of Pediatrics guidelines for relief of pain and anxiety in the Emergency Room recommend use of ibuprofen monotherapy first, acetaminophen monotherapy as a second-line agent, and acetaminophen with oxycodone as the third recommended option. Previously, acetaminophen with codeine was the recommended combination product. Acetaminophen in combination with codeine is not effective in one third of all children. Analgesic effect from ibuprofen is equal to codeine with or without acetaminophen.[5]

The table below provides dosing recommendations for combination acetaminophen and narcotic products. The acetaminophen content requires dosing every 4-6 hours. The dosing intervals for codeine, hydrocodone, and oxycodone monotherapy may differ.

Acetaminophen with	Dosing for Children Weight < 50 kg	Dosing for Children Weight >/= 50 kg*	Adult Dosing	Max per Dose for Children
Codeine	0.5-1 mg/kg codeine every 4-6 hours	30-60 mg codeine every 4-6 hours	30-60 mg codeine every 4-6 hours	60 mg codeine
Hydrocodone	0.1-0.2 mg/kg hydrocodone every 4-6 hours	10 mg hydrocodone every 4-6 hours	1-2 tabs every 4-6 hours	Limited by acetaminophen content
Oxycodone †	0.05-0.15 mg/kg oxycodone every 4-6 hours	5-10 mg oxycodone every 4-6 hours	5 to 15 mg oxycodone every 4-6 hours	10 mg oxycodone every 4-6 hours

* 50 kg (101 pounds) weight at approximately 14 years of age

† Oxycodone is not recommended in children younger than 6 years of age

References:

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4. Food and Drug Administration. Acetaminophen prescription combination drug products with more than 325 mg: FDA statement – Recommendation to discontinue prescribing and dispensing. Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm381650.htm. Accessed 4/18/2014.
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