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Archived newsletters:
Will soon be available on a website. Link will be available in the next issue.

FYI:
IV acetaminophen is non-formulary at the present time for SMH and HH. It is under review and being piloted in a targeted population at URMC Surgery Center (Sawgrass). The inpatient status continues to be a topic of discussion and the plan is to review the drug again soon at a Therapeutics Committee meeting.

URMC Therapeutics Committee:
This is a joint committee of Strong and Highland Hospitals. Each month, this newsletter will present updates on topics brought before the committee. This may be done by providing brief bulleted items on topics covered by the committee or with a link to a site to find more information.

Next Issue:
Drugs:
Year in Review

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PAIN MANAGEMENT WITH ACETAMINOPHEN

Acetaminophen (APAP) is a common analgesic and antipyretic with many uses including acute and chronic pain conditions, febrile illness in children, and for patients in whom aspirin or other NSAIDs are contraindicated (e.g. peptic ulcer or ASA allergy). APAP is readily available alone or in combination with other drugs, both over-the-counter and by prescription, and is often prescribed to hospitalized patients for the treatment of mild and moderate pain. This article reviews some of the characteristics of acetaminophen, its toxicity, and ways to use it more effectively.[1]

What is the mechanism of action?

While the exact mechanism remains unknown, acetaminophen is thought to work in the central nervous system by inhibiting both COX-1 and COX-2 enzymes, particularly COX-2, indirect activation of cannabinoid receptors, and through activation of descending serotonergic pathways.[2]

Does acetaminophen have an anti-inflammatory effect similar to NSAIDs?

No, it is thought to be mainly an antipyretic and analgesic agent working centrally and thus lacks the significant GI side effects that are often seen with NSAIDs.[2]

Is there evidence of cumulative toxicity?

APAP is thought to be safe when taken chronically without fear of cumulative effects or exacerbation of stable chronic liver disease, if the dose is within the recommended maximum daily dose. However, in patients with severe liver disease or malnutrition, or in children with inborn errors of metabolism leading to glutathione deficiency, a decreased dose should be considered.[2]

How effective is acetaminophen at relieving pain?

Comparison to morphine is often used as a standard for analgesic efficacy. For example, a moderate dose of morphine, given intramuscularly, appears to be slightly more effective than acetaminophen given by mouth. Specifically, in order to obtain at least a 50% reduction in pain, the number needed to treat for morphine 10 mg IM was 2.9, while acetaminophen 1000 mg PO was 3.8.[3]

Is acetaminophen available in an IV formulation?

The FDA recently granted approval for Cadence Pharmaceuticals, Inc., to market an IV formulation of acetaminophen called Ofirmev for treatment of fever and post-operative pain. It is currently the only IV formulation of this drug available in the US.[4]

In knee and hip surgery, IV acetaminophen plus morphine PCA led to better pain relief and less opioid use compared to placebo plus morphine PCA.[5] The IV formulation achieves a therapeutic plasma level more rapidly than PO which could be beneficial in acute settings such as post-operative pain. An IV dose of 1 gram administered as an infusion over 15 minutes will provide therapeutic plasma levels for approximately two hours.[2]

How can I use acetaminophen more effectively for my patients?

When APAP is prescribed, make sure the patient is actually receiving the drug (i.e., if the patient is having around-the-clock pain, then around-the-clock dosing, not PRN, should be used). When combination products such as Percocet or Vicodin are prescribed, if a dose is held due to opioid-related side effects, such as itching, excessive sedation or respiratory depression, the patient also misses out on the acetaminophen. To avoid this, order the opioids and APAP separately. For example, schedule the acetaminophen 650 mg every 6 hours and the oxycodone 5mg every 3-4 hours as needed for breakthrough pain. Then, if the patient has increased pain, the time interval for the oxycodone can be shortened without acetaminophen toxicity concerns.

References:

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Acetaminophen Toxicity

Is acetaminophen toxicity common?

Acetaminophen (APAP) was involved in over 150,000 exposures called into US Poison Centers in 2009. Locally, at Strong Memorial and Highland Hospitals, APAP was a factor in almost 20% of the cases seen as bedside Toxicology Consults.[1]

What is the toxic dose of acetaminophen?

Toxicity depends upon several factors including total dose, duration of dose, and patient-specific factors that may increase risk of toxicity (see below). Most toxicity and specifically deaths attributed to APAP are not from single acute doses of acetaminophen. Single acute doses of 7.5 grams or less should not cause hepatotoxicity in most adult patients.[2] The dose that would be expected to achieve a level of 200 mcg/ml (threshold of probable toxicity at 4 hours on Rumack-Matthew Nomogram) in a 70 kg adult is 14 grams. If taken over an extended duration, however, acetaminophen can potentially cause severe problems and death at doses just above the recommended daily maximum.

What situations can increase risk of toxicity?

- Alcoholics
- Malnourished patients
- Patients with preexisting liver disease (although this is not a cause for completely excluding these patients from taking APAP)
- Excessive dosing of APAP (i.e., multiple sources of acetaminophen or abuse of APAP products, e.g., APAP/opioid combination drugs)
- Chronic supratherapeutic use of APAP products

What types of exposures to acetaminophen lead to toxicity or death?

Most patients who suffer toxicity do so by taking chronic, excessive doses of acetaminophen. There are well over 100 products on the market that contain acetaminophen, either alone or in combination with other drugs. Patients who take acetaminophen as a deliberate act of self-harm are also at risk for toxicity if they exceed doses of 7.5 grams in a single administration. Most patients who take acetaminophen as part of a drug overdose can be effectively treated and toxicity prevented unless significant delays to treatment in a hospital setting occur.

How does acetaminophen actually cause toxicity?

Acetaminophen is normally metabolized through the sulfation and glucuronidation pathways in the liver. When these pathways are saturated, metabolism by the P450 pathway (specifically 2E1) takes over and increases the production of a highly reactive metabolite, N-acetyl-p-benzoquinoneimine (NAPQI), which quickly depletes the natural protective stores of cellular glutathione. This metabolite is a free radical. It binds to and thus disrupts cell proteins, causing cell death. Liver toxicity develops and signs and symptoms of toxicity such as anorexia, nausea, abdominal pain and vomiting are the most common effects. Some individuals also metabolize acetaminophen in their kidneys and nephrotoxicity may be seen as well. Severe acetaminophen toxicity can result in LFT's >10,000 IU/L, coagulopathy, hepatic encephalopathy, renal failure, and eventually fulminant hepatic failure, multiorgan failure, and death.

How is acetaminophen toxicity treated?

The antidote is N-acetylcysteine (NAC). NAC is available as an oral preparation as well as intravenously as Acetadote. If administered within 8 hours of the ingestion, NAC has been shown to be nearly 100% effective at preventing liver toxicity.[2] For the patient who presents >8 hours post ingestion with a toxic acetaminophen level, NAC should be started immediately to prevent further liver damage. NAC works by replenishing glutathione stores and scavenging free radicals related to acetaminophen toxicity and cell death.

How do I know if my patient needs NAC?

NAC is typically administered in the hospital setting. After a single, acute ingestion, the Rumack-Matthew Nomogram can provide information required for determining the need for NAC. At 4 hours post ingestion, for example, a level of >200 mcg/ml is toxic and requires treatment with NAC.

If the ingestion is chronic or if the time of ingestion is unknown, the nomogram cannot be used. In these situations, patient history, APAP level, LFTs, and coags are all used to determine risk.

Questions often arise regarding whether a patient's use of acetaminophen is potentially toxic. You can contact the Poison Center (1-800-222-1222) or request a Toxicology Consult (278-8161) if the patient is hospitalized, or talk with Drug Information at Strong (275-3232) if not, for help with this situation.

References:

1. Bronstein et al. 2009 Annual Association of Poison Control Centers' National Poison Report of the American Data System (NPDS): 27th Annual Report. ClinicalToxicology (2010) 48, 979–1178.
2. Nelson et al (2011). Goldfrank's Toxicologic Emergencies, 9th ed. McGraw-HillCompanies.

Acetaminophen Dosing

In 2009, the FDA appointed an Advisory Committee to take up the issue of acetaminophen toxicity and make recommendations to the FDA.

Although one of the recommendations of the committee was to lower the maximum daily dose (MDD) of acetaminophen, the FDA has chosen to leave the MDD at 4000 mg. per day for adults.

On July 28, 2011, McNeil Consumer Healthcare, makers of Tylenol brand products released a statement announcing that they would be changing the directions on the packages of Extra Strength Tylenol 500 mg to read: maximum dose of 6 per day instead of 8 (i.e., MDD 3000 mg per day instead of 4000 mg).

On January 13, 2011, the FDA issued an announcement directing drug manufacturers to limit the amount of acetaminophen in combination prescription products to 325 mg per dosage unit. Combination prescription products containing more than 325 mg of APAP have not been recalled. Instead, the FDA is allowing drug manufacturers some time to deplete their present stock. Most of these combination prescription products are APAP/opioid.

Earlier this year, Consumer Healthcare Products Association (CHPA) member companies voluntarily decided to convert all of the single-ingredient acetaminophen liquid products for children to a single concentration (160 mg/5 ml). The products will include flow restrictors that will make it more difficult for children to accidentally ingest the product. Syringes and standardized dosing devices will be packaged with these products for infants and children. For more information on changes to pediatric product labels and packaging, visit: http://rihealthnews.blogspot.com/2011/15/acetaminophen-dosing-fda-advised-to.html