Author: Alex Cohen, MD // Editor: Larissa Velez, MD

Acetaminophen and Overdose

I recently spent 2 weeks on the toxicology service at our hospital where we would follow-up with poison control center cases from the prior day as well as discuss each case with the fellows and attendings at rounds. Throughout my time on this rotation, one thing became clear to me: I will see acetaminophen overdoses and therapeutic misadventures, and I will need to know how to properly handle them. With this in mind, here's a review of what to do.

Background

To begin, and for completeness sake, APAP, the term used here, stands for N-acetyl-p-aminophenol (shortened to acetaminophen). This compound is an **analgesic and antipyretic with weak anti-inflammatory and antiplatelet properties**. It exerts its effects as a **central, indirect inhibitor of COX-2 enzymes** with only minimal peripheral COX-2 and COX-1 inhibition. Its antipyretic and analgesic effects are mediated by this central COX-2 inhibition, which leads to a decrease in PGE2 synthesis.

After absorption, about **90% of APAP is hepatically conjugated and eliminated in the urine**, but a small fraction is oxidized by CYP3A4 and CYP2E1 to form N-acetyl-p-benzoquinoneimine (NAPQI). **NAPQI is usually combined with glutathione to form nontoxic cysteine or mercaptate conjugates which are eliminated in the urine** as well. However, **in overdose, the rate and quantity of NAPQI formation overwhelms the supply of reduced glutathione. The end result is free NAPQI that can bind hepatocytes and result in hepatotoxicity**.

Clinical Manifestations

Although clinically not relevant, there are 4 stages after an acute APAP overdose. Stage 1 is marked by **nausea, vomiting, malaise, pallor, and/or diaphoresis,** while transaminases, or LFTs, remain normal. Stage 2 represents the onset of liver injury and is initially **marked by elevations in AST** (before elevations in ALT or INR). This commonly occurs within 24 hours and will definitely be seen **within 36 hours**. Of importance, the true definition of APAP-induced hepatotoxicity is peak AST above 1,000 IU/L. Stage 3 is the time of maximal hepatotoxicity and commonly occurs between **72-96 hours**. Signs and symptoms of fulminant hepatic failure include **encephalopathy, coma, and coagulopathy**. At this stage, prognosis is based on abnormalities of PT/INR, glucose, lactate, and pH. Finally, if the patient makes it past stage 3, stage 4 is considered the **recovery phase**. Most laboratory values will begin to normalize by one week and survivors will have complete hepatic regeneration without chronic liver dysfunction.

Who do we treat?

First, it is good to know that the minimum dose in an 8-hour span considered to cause overdose in an average-sized adult is **7.5g**. A useful number to remember is 150 mg/kg as a toxic dose of APAP. Patient reports of ingestion, however, can be unreliable and therefore the **Rumack-Mathew nomogram** has been adapted. Once a patient has been determined to be at risk, the next step is to determine a **serum APAP concentration at**

least 4 hours after ingestion and to plot this value on the nomogram. If the value falls **on or above** the treatment line, then therapy with N-acetylcysteine (NAC) should be started. NAC needs to be ideally started **within 8 hours post-ingestion. After 8 hours, the efficacy of NAC starts declining from an initial 100%**. **If an APAP level cannot be obtained before 8 hours (or if a patient arrives after the 8 hour mark), a loading dose of NAC should be given empirically**.

Treatment

If the patient presents prior to 4 hours post ingestion, activated charcoal may be used for decontamination. However, the GI absorption of APA is fairly rapid, so it is likely that charcoal will not be that effective after 1-2 hours post-ingestion. After 4 hours post ingestion, the treatment of choice is NAC, which mainly acts to **detoxify NAPQI and decrease available free NAPQI**. NAC can be given IV or PO in 2 separate protocols. The IV protocol is a **21-hour protocol** of a 150mg/kg loading dose over 15-60 min, followed by a 4 hour infusion of 12.5mg/kg/hr (50 mg/kg over 4 hours), followed by a final 16 hour infusion of 6.25mg/kg/hr (100 mg/kg over 16 hours). On the other hand, the PO protocol is a **72-hour protocol** that involves 18 total doses of NAC. Start with a loading dose of 140mg/kg followed by a 70mg/kg dose every four hours for 17 doses. Oral NAC has a fairly bad flavor, and is often vomited. It is advisable to use antiemetics prior to dosing the oral NAC. The decision to use the IV or PO protocol is up to the clinician and is mainly based upon the type of ingestion (acute vs chronic) and the patient's ability to tolerate PO. In general, the 21-hour protocol is simpler and shorter, and has similar clinical outcomes, so is the preferred one for single, acute acetaminophen overdoses.

Resources:

1. Hendrickson RG. Chapter 34. Acetaminophen. In: Nelson LS, Lewin NA, Howland M, Hoffman RS, Goldfrank LR, Flomenbaum NE. eds. *Goldfrank's Toxicologic Emergencies, 9e* . New York, NY: McGraw-Hill; 2011.http://accessemergencymedicine.mhmedical.com/content.aspx?bookid=454&Sectionid=40199408. Accessed September 24, 2014.

2. Hendrickson RG. Chapter 148. Acetaminophen. In: Marx JA, Hockberger RS, Walls RM. *Rosen's Emergency Medicine Concepts and Clinical Practice, 8e.* New York, NY: Saunders; 2013.

3. Heard K, Dart R. *Acetaminophen poisoning in adults: treatment*. In: UpToDate, Traub SJ (Ed), UpToDate, Waltham, MA. Available at: http://www.uptodate.com.foyer.swmed.edu/contents/acetaminophen-paracetamol-poisoning-in-adults-treatment?source=machineLearning&search=apap+overdose&selectedTitle=2~150&sectionRank=1&anchor=H4#H4. Accessed September 25, 2014.