Winter 2012-13

Reading

CEPCP

Professional Development:

Non-prescription drug overdoses

Non-prescription drug overdoses

After a day of steady and at times, heavy rain the clouds were starting to break and the rain had stopped. The passing of the cold front was leaving the air crisp and chilly. The combination of the sunset, the breaking cloud-cover and the shiny wetness of the cityscape was making the most mundane street glow and glisten like the pages of a tourist brochure.

The shift had been the usual Monday-busy with a wide variety of low acuity calls. Most of the mental effort had been spent trying to figure out how to keep the stretcher from getting soaked. The recent stop at Tim Horton's was now spreading the pleasant aroma of fresh coffee through the cab of the ambulance, adding to the fall ambiance.

"4411 call." the radio startled you, an afternoon lull had left the air strangely quiet long enough to now make the sound of the radio sound harsh.

"4411, go ahead". You were hoping it was a stand-by, it would be nice to actually drink the coffee while it was warm.

"4411, I have a priority four for you. It will be in the area of King St and Church St. Address of 97 Holmcrest Ave. You are going there for a 17 year old female, possibly overdosed on a pain medication. Unknown quantity. She is described as not alert, with shallow breathing. UTM is...". The dispatcher continued with the rest of the details.

As your partner began the drive to the address you slipped on some examination

gloves, grabbed the stethoscope off the dash and hung it around your neck.

Your thoughts began exploring the call. What type of pain reliever? Are there any special treatment considerations?
"I'm going to bet this is an opiate overdose". You say to your partner, the walking textbook.
"Very likely, given the call info", she agreed.

Any further ponderings or discussions were put on hold as you got waved down by a concerned looking middle aged man outside 97 Holmcrest Ave.

Introduction

This review will provide a breakdown of some common non-prescription drugs, their toxicity levels, overdose signs, and treatment considerations. We will provide some very valuable information that you need to confidently deal with these common and potentially lethal overdoses.

Although the number of non-prescription drugs that can pose a hazard is far too extensive to be covered in a brief review such as this, we will cover four of the most common ones; acetaminophen, acetylsalicylic acid (ASA), dimenhydrinate and diphenhydramine. So common that many believe they are harmless. It may surprise you how dangerous these drugs can be, some experts even argue that ASA and acetaminophen should only be available through a prescription (Brune, Hinz & Otterness, 2009).

Acetylsalicylic acid

Aspirin was first patented in 1900 almost 50 years after chemists first discovered how to isolate the active ingredient (salicin) from willow bark and buffer it with sodium and acetyl chloride to make acetylsalicylic acid (ASA).

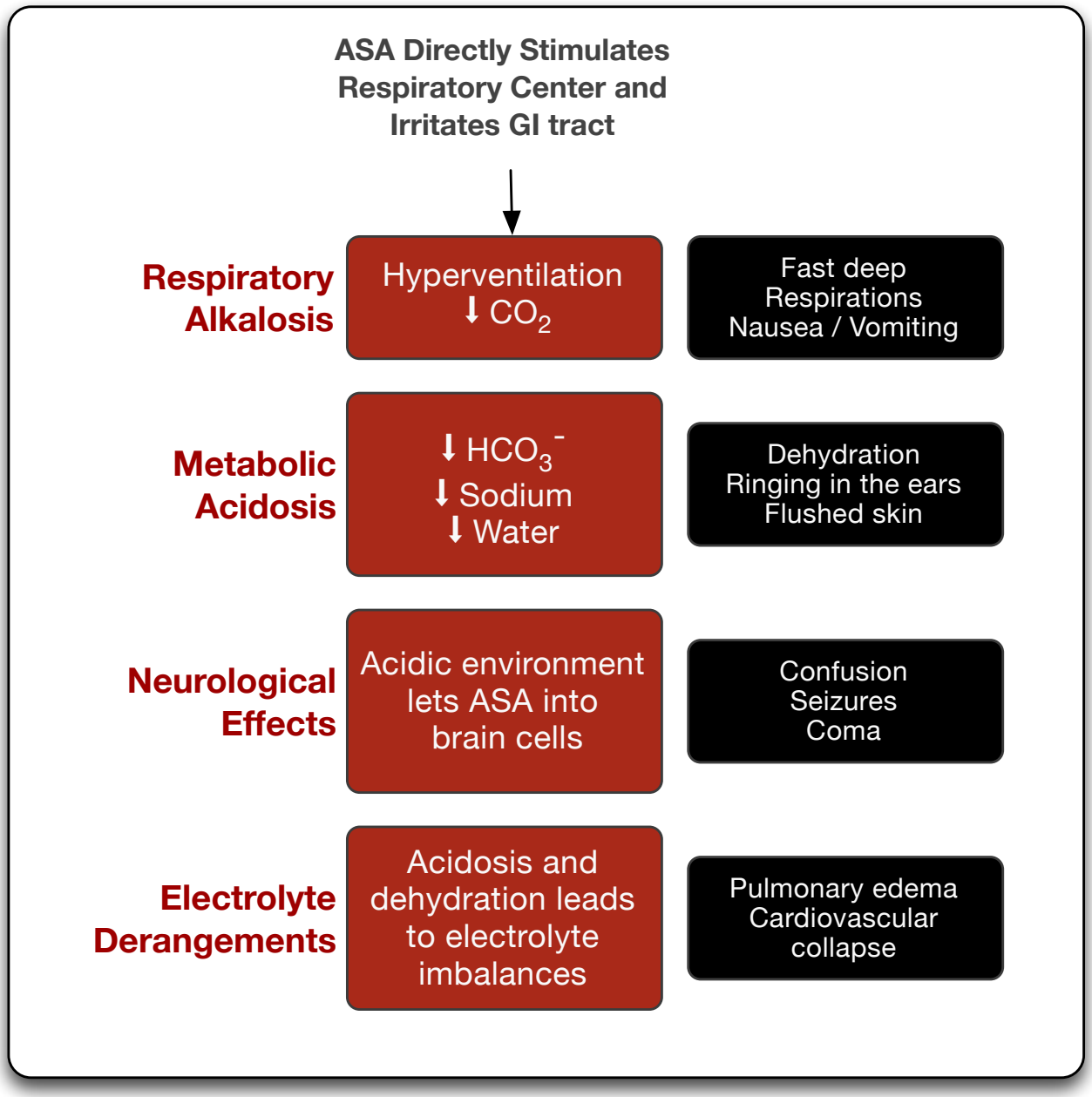
Today there are over 20 non-prescription products and many more prescription medications that contain ASA. Many other non-drug related products also contain salicylates including some cosmetics, sun blocks and wintergreen scented oils. Clearly, with such a massive product availability added to its reputation for being very safe, the potential for intentional or accidental overdose is large.

Basic Pathophysiology

When toxic levels of ASA are ingested the drug directly stimulates the respiratory center in the brain causing hyperventilation with subsequent decreased CO_2 levels in the lungs and the blood (Kamanyire, 2002). The decreased CO_2 level moves the body's pH level towards alkalosis (Kamanyire, 2002). The kidneys begin to compensate for the alkalosis by excreting bicarbonate (which acts as the base, or buffer, in the body). Along with the bicarbonate, sodium and water is also excreted (Kamanyire, 2002). The end result is dehydration from sodium and water loss (Kamanyire, 2002). However, more importantly, the excretion of bicarbonate often leads to acidosis after 12-24 hours. Since the acidosis

is caused by the kidneys it is considered metabolic acidosis (Kamanyire, 2002).

The acidic environment in the body changes the ability of ASA to cross the blood-brain barrier essentially providing the ASA with the key to enter the brain-cells and wreak havoc. The ASA causes neurological symptoms ranging from drowsiness to convulsions (Kamanyire, 2002; Drummond, Kadri & St-Cyr, 2001). But there is more, the ASA also interferes with energy (ATP) production in the cells causing them to use more oxygen and produce more CO_2 (Kamanyire, 2002). The cells, straining to keep up with energy demands and with ASA interfering, end up overheating causing the patient to become hot, flushed and sweaty, further worsening the dehydration (Kamanyire, 2002). The fluid loss from ASA toxicity is significant and can reach 4-5 liters for the average adult in a moderate overdose and as much as 8-10 liters in severe cases (Temple, 1978). In addition, the dirty, strained cellular metabolism also generates other acids further worsening the acidosis (Temple, 1978).

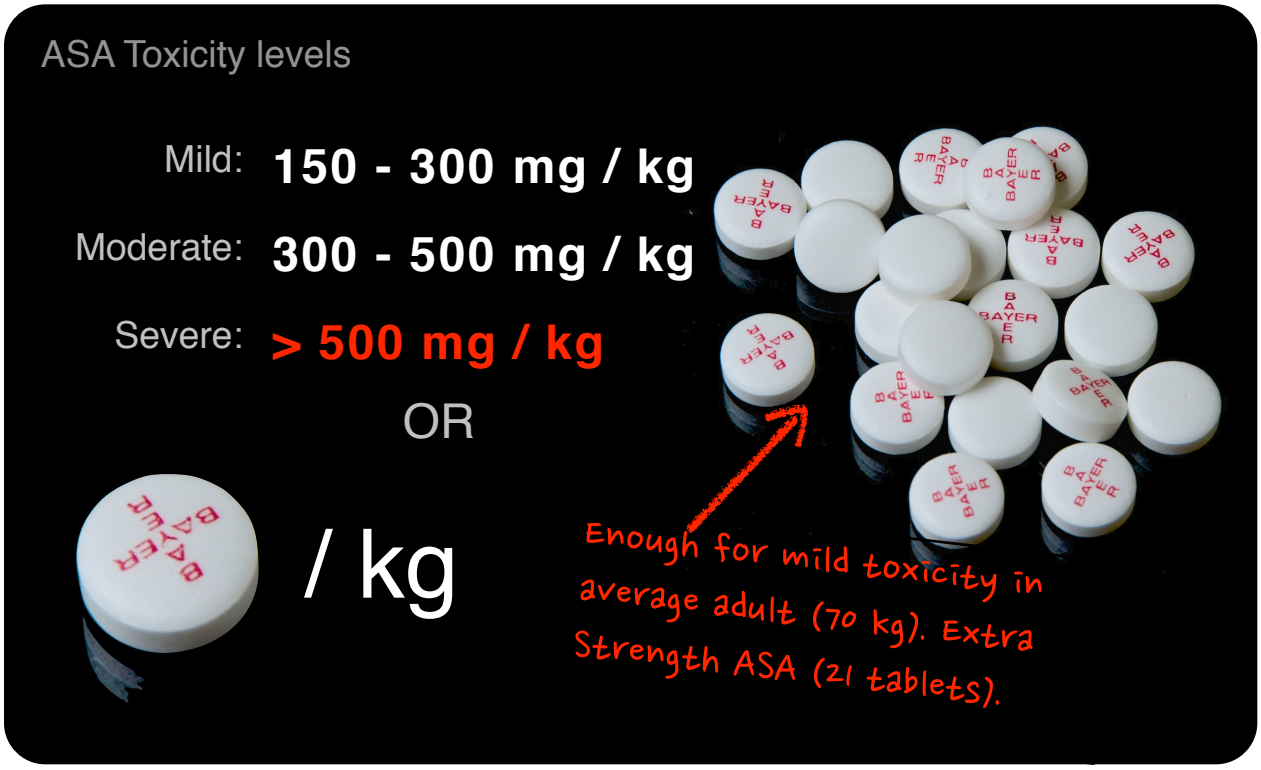


As a result of all this mayhem, electrolyte imbalances can occur in almost any direction with most patients having high sodium levels while some have dangerously low levels (Temple, 1978). The usual causes of death from an ASA overdose are brain dysfunctions, cardiac failure or pulmonary edema (Temple, 1978).

Overdose levels

150 - 300 mg/kg of ASA has been shown to cause mild to moderate toxicity, 300-500 mg/kg serious toxicity and more than 500 mg/kg has the potential of being fatal (Kamanyire, 2002). The math is consequently pretty easy since an extra strength ASA tablet usually contains 500 mg of ASA (regular strength is 325 mg). Basically one tablet per kg is enough to be in the moderate to serious range. Less than 150 mg/kg has not been shown to have any toxic effects, so less than half a tablet per kg is probably not going to be serious (Kamanyire, 2002). However, ASA doses greater than 1,000 - 2,000 mg (3-6 normal ASA tablets) saturates the normal excretion pathways leading to a gradual accumulation of ASA in the body (Chyka et al. 2007). Consider this if you encounter a patient who may be taking too much ASA either due to confusion or from thinking 'more is better' and subsequently increasing their dosing.

Oil of wintergreen is, as the name implies, oil that is refined from the wintergreen plant. The oil has a wide variety of uses including pest control, topical pain-relief ointments and flavoring extract. The oil contains a concentrated amount of an ASA-like substance called methyl salicylate. Because of its concentrated nature and pleasant smell it can pose a significant danger to children. Experts suggest any more than a 'lick' by children less than 6 years old, or the ingestion of over 4 ml in patients older than 6 can pose a risk of toxicity (Chyka et al. 2007).



Signs and Symptoms

Signs and symptoms following an ASA overdose will start anywhere from 1-24 hours after ingestion but most commonly occur within 4-8 hours (Chyka et al. 2007). Mild symptoms consist of nausea, vomiting, epigastric pain, ringing in the ears and flushing (Kamanyire, 2002; Drummond, Kadri & St-Cyr, 2001). Moderate signs consist of hyperventilation (both rate and depth), deafness, tremors and sweating (Kamanyire, 2002; Drummond, Kadri & St-Cyr, 2001). Severe signs are predominated by neurological effects including drowsiness, confusion, seizures or coma (Kamanyire, 2002; Drummond, Kadri & St-Cyr, 2001). In some severe cases pulmonary edema or cardiovascular collapse may occur (Kamanyire, 2002; Drummond, Kadri & St-Cyr, 2001).

ASA and Reye's syndrome

Public warning poster regarding ASA and Reye's syndrome (date unknown).

Reye's syndrome is a puzzling disease that occurs mostly in children. In 1980 researchers discovered a link between ASA and Reye's syndrome (Starko et al. 1980). It appeared that when children took ASA during certain types of viral illnesses an abrupt onset of vomiting, brain dysfunction and liver failure occurred (Starko et al. 1980). Researchers believe that the ASA acts as a cofactor during the viral illness and triggers the devastating disease (Glasgow, 2006). A public information campaign ensued, warning parents and physicians about the dangers of giving ASA to children with suspected viral illnesses. Authors are calling the effectiveness of the public information campaigns nothing short of remarkable in reducing the number of cases world wide (Glasgow, 2006). However, concerns remain that the lesson learned may fade from memory and parents or patients may again use ASA to treat a fever caused by viral illness and trigger Reye's syndrome (Glasgow, 2006).

Prehospital treatment

The focus in the prehospital field when dealing with an ASA overdose is on the recognition of the overdose, an accurate estimation of the time when the ingestion occurred and the quantity ingested. An early update to the receiving facility with all the details pertaining to the ingestion and the signs and symptoms exhibited will help the ER staff get ready to treat the patient quickly.

Clearly, continuous cardiac monitoring, frequent chest auscultation and accurate respiratory counts are key assessment parameters that need to be closely monitored. A blood sugar measurement is warranted if the level of awareness is altered as hypoglycemia can occur as a result of the ASA toxicity.

Acetaminophen

Acetaminophen was first marketed in 1955 as Tylenol Elixir for children. However, it didn't take long for the drug to become the leading pain killer in North America. Tylenol has been marketed very successfully as a safer alternative to ASA as it causes less gastric irritation and does not seem to trigger Reye's syndrome in children. However, safer is a relative term considering that acetaminophen toxicity is the leading cause of liver failure in North America and carries a 30 percent mortality rate (Hornsby et al. 2010; Schiodt et al. 1997; Lee, 2007).

Many drug names provide clues that they contain acetaminophen. Look for the **CET**:

A**CET**aminopen
Oxyco**CET**
Perco**CET**
Endo**CET**
Hydro**CET**
Robaxa**CET**
Trama**CET**

The patent for acetaminophen held by McNeil laboratories (that is now owned by Johnson & Johnson) has long since expired and acetaminophen is now available in many generic brands. There are between 200 - 300 drugs that contain acetaminophen so the accessibility and overdose potential is significant. Acetaminophen toxicity generally occurs in one of two ways, either a patient is trying to commit suicide and takes a large quantity of acetaminophen all at once (acute ingestion), or patients take a bit more than recommended, either by increasing the dose or by taking more frequent doses. In addition, some patients may take more than one drug that contain acetaminophen without realizing it. In fact, around half of all acetaminophen overdoses are unintentional (Hornsby et al. 2010).

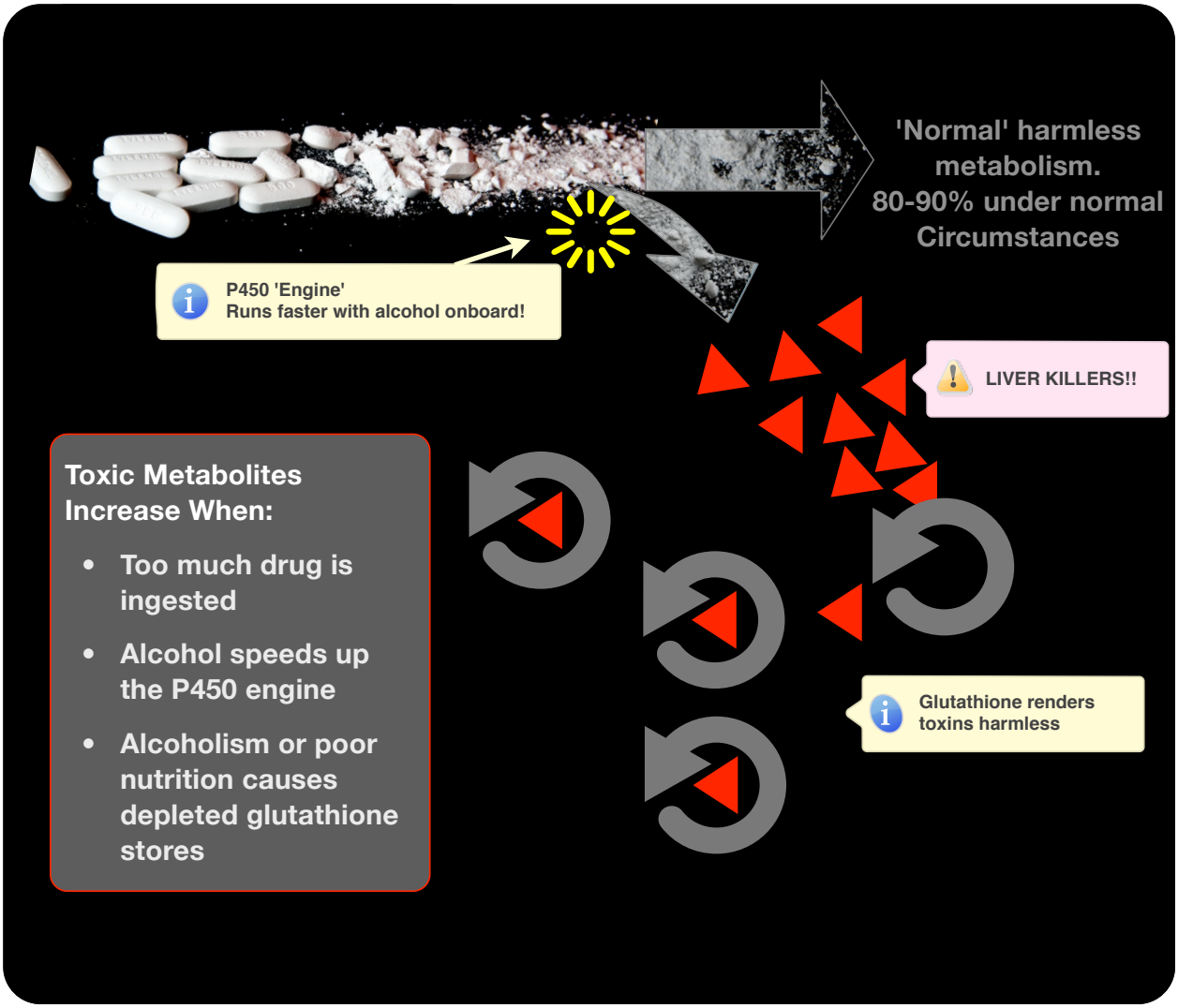
One of the contributing factors is that the public is poorly educated about the safety

of acetaminophen. In an American study conducted in 2010 less than half of the people polled knew that acetaminophen and Tylenol was the same thing (Hornsby et al. 2010). Furthermore, one in ten thought that ingesting harmful amounts of acetaminophen was difficult or impossible (Hornsby et al. 2010). Ironically the unintentional overdoses carry the highest mortality rate (Gyamlani & Parikh, 2001; Schiodt et al. 1997). It is believed that the higher mortality rate is due to those patients presenting to the ER later than the intentional overdoses (Gyamlani & Parikh, 2001; Schiodt et al. 1997).

Basic Pathophysiology

When acetaminophen enters the body the majority of the drug gets metabolized into harmless substances, some of it gets excreted unchanged, and a small (5 percent) portion gets sucked through an enzymatic engine (P450) that turns the harmless drug into a lethal poison that destroy liver cells (Gyamlani & Parikh, 2001).

Luckily, the body has a store of protection (Glutathione) against these killers (Rumack & Matthew, 1975). The Glutathione binds to the harmful acetaminophen metabolites and escorts them out of the body before they can do any damage (Rumack & Matthew, 1975). Like a



crew of highly trained bouncers that can spot the trouble-makers and escort them out before they start causing problems.

Toxicity occurs when there is more drug than what the Glutathione can take care of, when that happens the toxic metabolites bind to the liver cells and kill them. Patients who consume alcohol activate the P450 engines to metabolize the alcohol and since the P450 'engines' are activated in those patients, more of the acetaminophen gets dragged in and converted into poison (Bonkovsky et al. 1994). To make matters worse, alcoholics and malnourished patients have a diminished store of Glutathione (Bonkovsky et al. 1994; Schiodt et al. 1997).

It is a disaster, more bad guys, less bouncers, the liver cells get slaughtered.

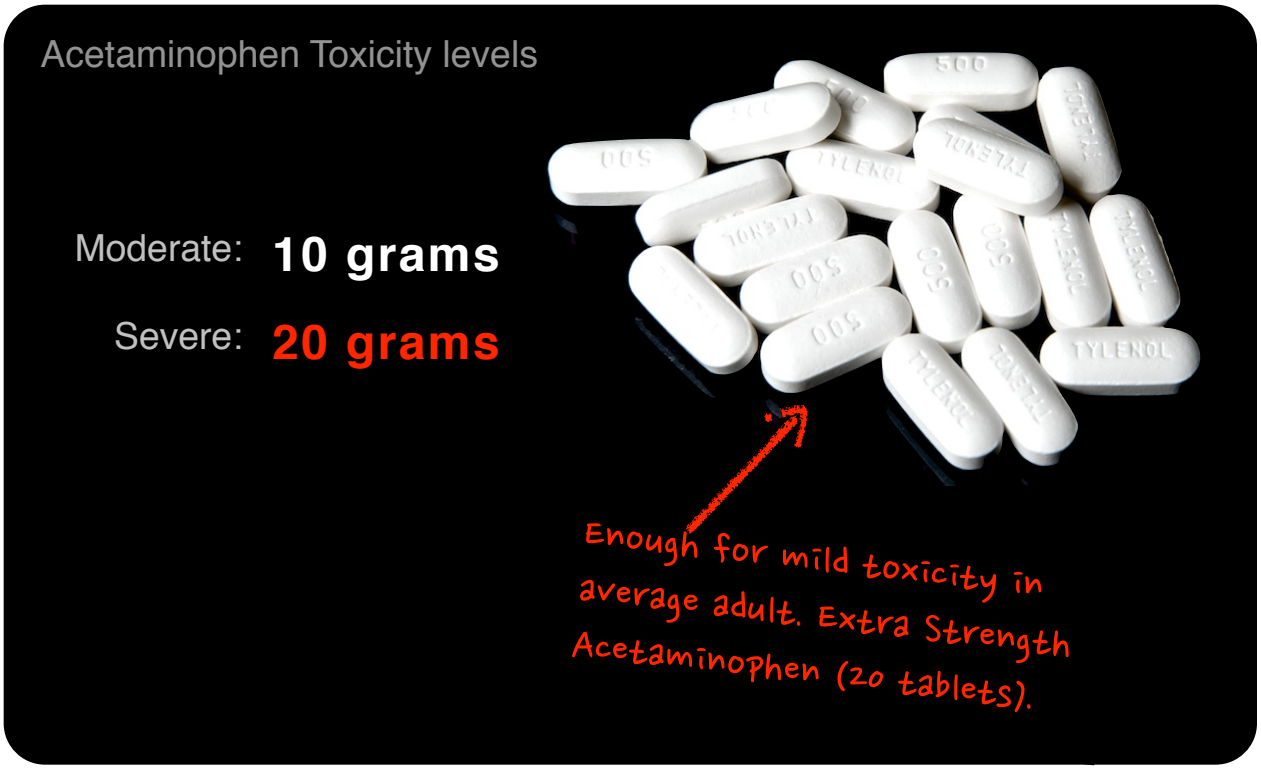
Overdose Levels

4 grams per day is the recommended maximum daily dose. 4 grams equates to 8 extra-strength tablets (they are typically 500 mg each) (Zimmerman & Maddrey, 1995; Schiodt et al. 1997). The toxic level for acute ingestions is 10 grams (20 tablets), with 20 grams carrying the potential of being lethal (Zimmerman & Maddrey, 1995).

However, acetaminophen can easily begin to accumulate in the body especially in a patient who is alcoholic or malnourished (as explained above) so even a daily dose of 3-6 grams (6-12 tablets) can cause liver damage in susceptible individuals (Bonkovsky et al. 1994).

Signs and Symptoms

The signs and symptoms of acetaminophen toxicity occur in three phases. It is important to be well aware of the indicators of acetaminophen toxicity since many of the acetaminophen overdoses are accidental and



the patient will have no idea why they are feeling so unwell. Phase one begins within hours of ingestion and the signs and symptoms are often quite vague. The patient may start feeling nauseous and will often lose their appetite (Rumack & Matthew, 1975). The general appearance is often a pale diaphoretic patient who appears quite ill (Rumack & Matthew, 1975). There are no neurological signs this early in the acetaminophen overdose so if the patient is unresponsive assume co-ingestion with other drugs (Rumack & Matthew, 1975).

The second phase occurs over the following 48 hours and the patient often begins to feel better (Rumack & Matthew, 1975). Some right upper quadrant abdominal pain may begin at this stage.

The third stage spans the 3-5 days after ingestion and is characterized by liver failure. Jaundice, coagulation defects and hypoglycemia. In addition, neurological signs, kidney failure and heart defects may begin to manifest at this late stage (Rumack & Matthew, 1975).

Treatment

The definitive treatment for acetaminophen overdoses is essentially to provide the body with extra protection against the toxic metabolites. The protection is available in a substance called N-acetylcysteine (Rumack, 2004). The treatment is effective up to 8 hours after the acetaminophen ingestion and may even hold some benefit as late as 24 hours after ingestion (Gyamlani & Parikh, 2001).

As prehospital providers recognition is again our biggest role. Trying to get an accurate estimate of the quantity and time of the ingestion can prove invaluable for the ED staff to further direct treatment. The good news is that in cases where we reach the patient shortly after the ingestion has occurred, it is unlikely that they will deteriorate en-route to the hospital.

However significant acetaminophen overdoses remain high acuity calls that warrant rapid transport and early hospital notification.

Dimenhydrinate / Diphenhydramine

Because most readers are more familiar with the names Benadryl and Gravol I will refer to diphenhydramine as Benadryl and dimenhydrinate as Gravol in this text. It is important to realize that these are trade-names and many drugs under other names contain dimenhydrinate and diphenhydramine.

Benadryl was first approved for use in 1946 and was initially only available with a prescription to treat allergy symptoms. Gravol, followed shortly after and was created by combining Benadryl with theophylline. Consequently Gravol is much less potent than Benadryl and has a slower time of onset (the Gravol has to dissociate from the theophylline before it begins to work). However, the overdose levels, symptoms and treatment are very similar so even though this section is written about Benadryl it also applies to Gravol.

Benadryl is a bit different from ASA and acetaminophen in that it can provide users with a high. Consequently it carries some abuse potential. As with the other drugs Benadryl comes in so many varieties and combinations that it is impossible to keep track of. There are over 20 different brand names and at least as many combination products used for anything from sleep-aids to cold relief. Also, Benadryl is available in a wide variety of topical creams and sprays whose absorption through non-intact skin can add to toxic levels of Benadryl.

Basic Pathophysiology

The pathophysiology of Benadryl overdoses is quite simple: (a) anticholinergic effects and, (b) cardiac effects from sodium channel blockade (Scharma et al. 2003). As you may recall from

previous professional development readings, anticholinergics are drugs that essentially block the parasympathetic nervous system (PNS). Given that the PNS is essentially the *brake* within the body that slow things down, blocking it causes the opposite effect. Many of us will recall a catchy rhyme from our college days that help us remember the typical signs of a anticholinergic overdose:

> *red as a beet, dry as a bone, mad as a hatter, hot as a hare, blind as a bat.*

This illustrates the flushed, dry, aggressive, overheated patient with dilated pupils. In addition we can expect the patient to have tachycardia, high blood pressure and rapid breathing.

The cardiac effects caused by the sodium channel blockade can cause serious, even lethal, dysrhythmias. The time of symptom onset can be as early as 30 minutes after ingestion but rarely occur after 4 hours (Scharman et al. 2006). If the toxicity is caused by an ointment or spray absorbed through the skin, the onset may be delayed as much as 8 hours (Scharman et al. 2006).

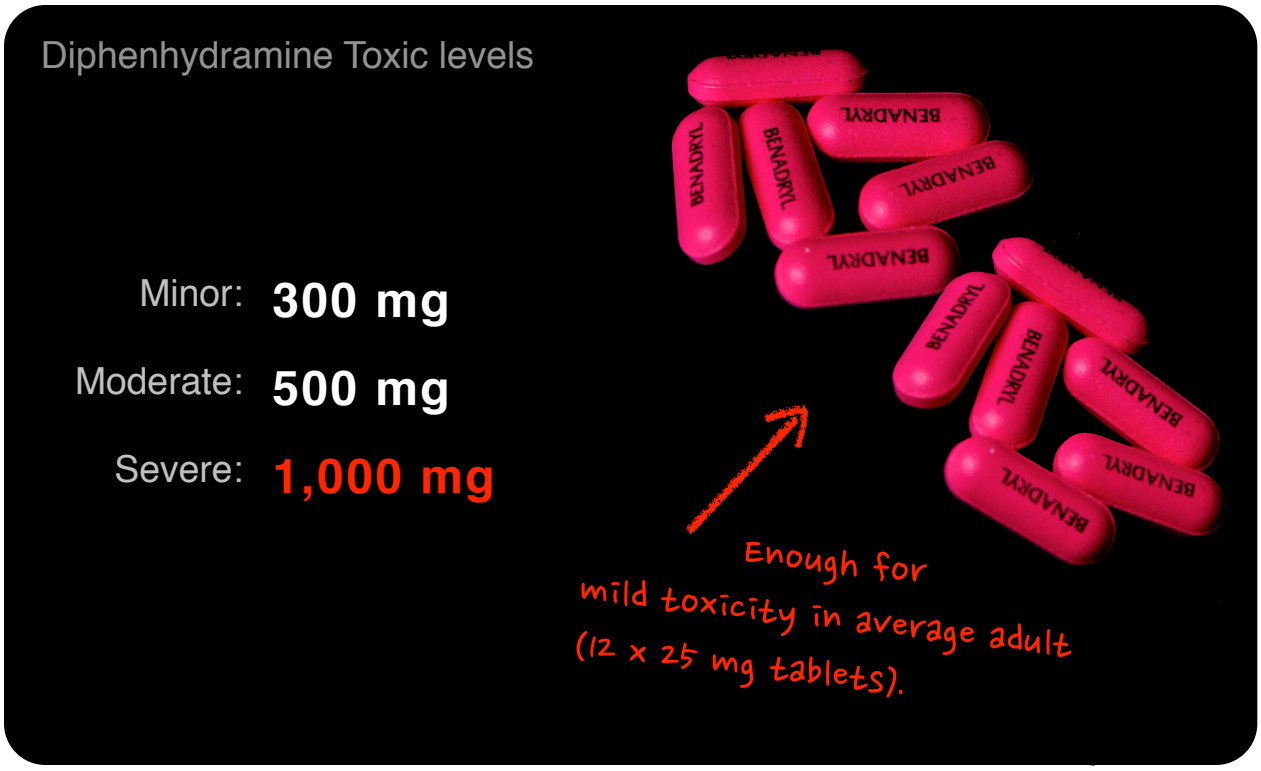
Overdose levels

The threshold level for Benadryl toxicity is 300 mg for an adult patient (Scharman et al. 2006). Most of the formulations contain 25 mg per tablet so 12 tablets is enough to cause a mild overdose.

A moderate degree of overdose is 500 mg (20 tablets) and severe levels are considered those over 1,000 mg (40 tablets) (Scharman et al. 2006). The toxicity can occur at lower doses in a patient that has been drinking alcohol or in someone who has pre-existing psychosis (Scharman et al. 2006).

Signs and Symptoms

Minor signs and symptoms include sleepiness, dilated pupils, dryness of the mouth, flushing, fever and tachycardia (Scharman et al. 2006).



Essentially these are mild anticholinergic symptoms along with the normal sedative effect of Benadryl that is present even at therapeutic doses.

At moderate overdose levels the sleepiness turns to agitation, mood swings with inconsolable crying, hallucinations and abnormal muscle movements (Scharman et al. 2006). The internet is ripe with user accounts from individuals getting high from Benadryl. The following was written by a user who took 400 mg of Benadryl and it occurred about 2.5 hours after the ingestion (there were other symptoms prior to this as well);

> *I start having severe moments of paranoia and depression. Just for about a few minutes at a time, I start thinking angry thoughts about my friends and my girlfriends, that they are evil and they are trying to play me. After a few minutes of this it goes away and I feel normal again, but it repeats a couple of times. At this point the twitching starts. I've never had these effects ever before and they were horribly uncomfortable. Laying on my back with my head on the pillow, my right leg begins to feel restless. Every 2-3 minutes I get an irresistable urge to twitch my right leg. And when I say twitch, I don't mean a little twitch, I mean a big tremor, like I was trying to kick a field goal or something. This continues every 2-3 minutes for about a half hour until I conclude that I'm not going to be able to get asleep from just closing my eyes. I decide that this trip has gone bad and it's time to abort.*
>
> *I get up and move to the bathroom and induce vomiting, throwing up the contents of my stomach. In the water, I can clearly see the 16 almost-completely dissolved benedryl tablets floating in the water. This terrifies me for some reason, and I quickly flush the toilet and walk to the sink to wash my mouth out. This is the first real detailed hallucination I see. As I look down towards the drain, I can clearly see a number pad on the drain, like the kind you see on movies attached to a nuclear warhead. I cock my head and look at it again, and I can still see it clearly but I realize that it's just a hallucination now and not really there.*

http://www.erowid.org/experiences/exp.php?ID=56587

At moderate overdose levels more significant cardiac dysrhythmias may begin to appear. The most common abnormality is a mild QRS widening (Scharma et al. 2003). In addition, a phenomena called Brugada syndrome may also appear as ST elevation in the septal and anterior leads (Lopez-Barbeito et al. 2005). The 'T' wave may also begin moving further away from the QRS complex putting the patient at risk for ventricular dysrhythmias (Scharma et al. 2003).

At severe overdose levels seizures, respiratory arrest and lethal arrhythmias may occur (Scharman et al. 2006).

Treatment

There are is no real antidote to Benadryl, but there are some treatments that may be helpful. Obviously if the patient is in seizure, immediate administration of a benzodiazepine is a key management strategy (Scharman et al. 2006).

If the patient is agitated a BHP patch for sedation orders is not a bad idea. Experts recommend the administration of sodium

bicarb if the QRS width is greater than 100 ms. Most CEPCP services do not currently carry sodium bicarb but if it is available it may be worth patching for (Scharman et al. 2006; Scharma et al. 2003).

Physostigmine is a drug that may be administered in the ED. It essentially interferes with the breakdown of the PNS neurotransmitter (acetylcholine) counteracting the anticholinergic effects of the Benadryl (Scharman et al. 2006).

As with the other drugs that we have reviewed, the information gathering on the scene and close monitoring and transport are the most important components that we can provide as prehospital providers.

On Holmcrest..

As you step out of the ambulance the gentleman is clearly very stressed;
"It is my daughter, she is barely conscious. I think she has tried to kill herself".

With a trembling hand he hands over a box with a pill bottle in it.

"She has taken a ton of these."

You and your partner remove the stretcher and are relieved to see that you can get it right up the shallow front step and into the house.
"Where is she, and whats her name?", you ask.
"Its Jessica, she is down here, in her bedroom."
You are led down the hall to a typical teenagers room. Jessica is laying on her stomach. You notice how flushed she appears. Her breathing seems regular and of a normal depth and rate. Your partner begins to work on setting up oxygen, monitor and getting vital signs. A painful stimuli elicits a moan and a half-hearted attempt at a punch.

You turn your attention to the father, you need some vital information.
"When, exactly, did she take the pills?"
"I don't know, we got a call from her friend she had texted her and told her she just took some pills, basically saying goodbye.". The father is frantically trying to suppress his tears, it is a losing battle.
You notice the iPhone in its purple case next to the patient on the bed. You hand it to the father.
"Can you check what time that was sent?".
"Sure", after a few failed attempts, due to his trembling hands, he is able to find the sent text message.
"Here it is."
You read the message.

Finally did it, will be over soon, tell Rich I love him, have a great life...bitch.

The message was sent at 4:16 pm. You check your watch it is 5:02, not quite an hour.
"Do you have any idea how many were in this." You ask the father, holding up the pill bottle. He is intently watching your partner work.
"Yes, it was full, I found the bag with the receipt, she must have just gotten them".

You quickly count the pills and find 55 pills left in the bottle, 25 missing.

The ingredients listed are Diphenhydramine 25 mg and Acetaminophen 500 mg. You realize you are seeing the early diphenhydramine effects and that things could quickly turn bad.

"She is tachy at 130, blood pressure is 146 over 94, sats are good, pupils are blown at around 7 mm, sugar is 7.2." Your partner says and hands you a cardiac strip. You look at it, paying extra attention to the QRS width, it still looks narrow.

"OK, lets get her moving quickly. I predict she may become combative shortly."

You thank the father for his help and explain the next steps. Some quick mental math makes you realize that Jessica has also ingested enough acetaminophen to be in the minor to moderate toxicity range. Given her small build you believe that she will probably need to be treated for that as well.

The trip to the hospital unfolded predictably. Jessica started hallucinating and was soon getting quite aggressive. The QRS width remained narrow and the heart rate did not increase much more. As early as practical you provided the ER with a thorough update including the time and quantity of drugs ingested. They were ready for you when you arrived.

It was almost a month later, again on shift, as you drove by the local high-school. The school had just finished for the day and you stopped at the crosswalk to let a flock of youths cross the street when you saw her. She was wearing a faded blue hoody, torn jeans and pink gloves. As she crossed in front of the ambulance she looked up and made direct eye contact, seemed to slow her pace for just a moment, waved quickly and kept walking, disappearing into the sea of students leaving the school.

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