

Acetaminophen Overuse

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Issues

- ...acetaminophen (commonly known as Tylenol®) has become the most widely used antipyretic and analgesic because of its efficacy and relative safety
- Although it is relatively safe when used at therapeutic doses, intentional and unintentional overdoses of acetaminophen have been recognized to cause fatal and nonfatal hepatic necrosis which can lead to acute liver failure.

Introduction

Since its introduction in 1950, acetaminophen (commonly known as Tylenol®) has become the most widely used antipyretic and analgesic because of its efficacy and relative safety. It is readily available in hundreds of over-the-counter and prescription medications. Although it is relatively safe when used at therapeutic doses, intentional and unintentional overdoses of acetaminophen have been recognized to cause fatal and nonfatal hepatic necrosis which can lead to acute liver failure. [1, 2, 3]

In 2005, 138,602 acetaminophen exposures were reported by the American Association of Poison Control Centers Toxic Exposure Surveillance System. Approximately one-half (49%) of these exposures were from acetaminophen alone, and one-half (51%) were from acetaminophen in combination with other drugs. Forty-six percent (46%) of the exposures were intentional. Thirty-one percent (31%) of the exposures occurred among children younger than six years, and twenty percent (20%) among children between 6 and 19 years of age. Additionally, 187 deaths were reported where acetaminophen was believed to be the primary responsible agent. Of these fatalities, 48 were associated with acetaminophen as a single agent, 47 with acetaminophen plus one or two other products, and 92 with acetaminophen in a combination product, usually containing an opioid. [4]

Pharmacokinetics

Acetaminophen is available over-the-counter in both immediate and sustained-release formulations. Acetaminophen, in varying strengths, is contained in over-the-counter cough, flu and cold, allergy and sinus, and sleep preparations. [1] Depending on the formulation, the liquid preparations may range in concentration from 32 mg/mL to 65 mg/mL (syrups, elixirs) to 100 mg/mL (infant drops), and the strength may range from 80 mg to 650 mg for pills, capsules, or suppositories. [5]

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Immediate release acetaminophen is rapidly and completely absorbed from the gastrointestinal tract, with peak plasma concentrations being reached from 70 to 160 minutes following ingestion of a therapeutic dose. However, following ingestion of extended-release preparations or with co-ingestion of other drugs or high carbohydrate foods which delay gastric emptying, peak serum concentrations may be delayed beyond four hours. The various suppository preparations have different absorption characteristics, and reach peak concentration at variable times. [1]

Following oral doses, acetaminophen is metabolized extensively in the liver via three main pathways: glucuronidation, sulphation, and oxidation. At therapeutic doses, 90% of acetaminophen is metabolized in the liver to sulfate and glucuronide conjugates that are then excreted in the urine or bile. One-half of the remaining acetaminophen, or 5%, is oxidized via the hepatic cytochrome P450 mixed function pathway to N-acetyl-p-benzoquinoneimine (NAPQI), which is a toxic metabolite. With normal doses, the small amount of NAPQI formed after ingestion is promptly detoxified by conjugation to hepatic glutathione, forming nontoxic compounds that are excreted in the urine. However, when toxic doses are ingested, the sulfate and glucuronide pathways become saturated resulting in an increased fraction of acetaminophen being metabolized by cytochrome P450 enzymes. As large amounts of NAPQI are formed, glutathione stores in the body are depleted. When approximately 70% of glutathione stores are depleted, unconjugated NAPQI begins to accumulate and hepatic injury ensues. [1, 2, 6]

Evaluation of Suspected Acetaminophen Toxicity

Prompt recognition of toxicity is essential to preventing morbidity and mortality associated with overuse of acetaminophen. [7] Therefore, a careful assessment and a detailed medical history of the patient are important when evaluating the potential for toxicity of an ingestion of acetaminophen. Important components include, but are not limited to, the age of the patient, concomitant medications or substances that may have been ingested, and risk factors that could increase the potential for toxicity, such as chronic alcohol abuse or malnutrition. The clinician should also consider contacting the local poison control center for reporting the toxicity and also to obtain any information that may assist in the proper treatment of the patient. Evidence suggests that children under the age of 6 years are less susceptible to the same amount of acetaminophen per unit of body weight than would be associated with severe toxicity in older patients. [8] An acute ingestion is often discovered quickly in younger patients, whereas older patients that may be attempting self-harm are more likely to conceal such an attempt.

The amount ingested, as well as the pattern and duration in which the medication was taken, must be determined as quickly and accurately as possible in order to correctly interpret laboratory values and administer appropriate therapy. The range of toxicity largely depends on how the medication was taken in terms of whether the ingestion was acute or chronic.

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Acute Ingestion of Acetaminophen

Acute toxicity of acetaminophen is generally regarded as a single ingestion over less than a 4 hour time period. [7] The risk of toxicity is best predicted by relating the time of ingestion to the serum acetaminophen concentration. Current guidelines recommend emergency room referral for an acute, single ingestion of acetaminophen under the following circumstances: [9, 10]

- The patient has symptoms of apparent acetaminophen toxicity such as protracted vomiting, upper right quadrant pain or mental status changes.
- The patient is less than 6 years old and has ingested 200 mg/kg or more.
- The patient is 6 years old or more and has ingested at least 10 g or 200 mg/kg (whichever is lower).
- The patient has ingested an unknown amount of acetaminophen.
- All patients should be referred to the emergency department for ingestions involving unknown intent, suspected or stated self-harm or possible malicious administration.

Table 1 [5]

Acetaminophen Dosing for Children						
Age of Child	Weight of Child	Dosage Recommendation	Acetaminophen Drops (80mg/tsp)	Acetaminophen 160 mg/tsp	Chewable Tablets (80 mg)	Adult Tablets
≤ 3 months	6 – 11 lbs	40 mg	½ dropperful (0.4 mL)	-----	-----	-----
4 – 11 months	12 – 17 lbs	80 mg	1 dropperful (0.8 mL)	½ tsp (2.5 mL)	1 tablet	-----
12 – 23 months	18 – 23 lbs	120 mg	1 ½ dropperful (1.2 mL)	¾ tsp (3.75 mL)	1 ½ tablets	-----
2 – 3 years	24 – 35 lbs	160 mg	2 droppersful (1.6 mL)	1 tsp (5 mL)	2 tablets	-----
4 – 5 years	36 – 47 lbs	240 mg	3 droppersful (2.4 mL)	1 ½ tsp (7.5 mL)	3 tablets	-----
6 – 8 years	48 – 59 lbs	320 mg	-----	2 tsp (10 mL)	4 tablets	1 adult tablet
9 – 10 years	60 – 71 lbs	400 mg	-----	2 ½ tsp (12.5 mL)	5 tablets	1 ½ adult tablets
11 – 12 years	72 – 95 lbs	480 mg	-----	3 tsp (15 mL)	6 tablets	1 ½ adult tablets

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Repeated Supratherapeutic Ingestion of Acetaminophen

Repeated supratherapeutic ingestions of acetaminophen (RSTI), frequently referred to as subacute or chronic, take place over a period longer than 4 hours. [8] Most commonly they are unintentional and could occur from (a) self-medication for pain or fever in doses exceeding professional medical recommendations or the package recommendation of 4 grams/day, (b) dose calculation and administration errors, and (c) use of multiple products that contain acetaminophen, any of which can lead to liver injury. [3, 11] Prevention of inappropriate dosing of acetaminophen includes education of patients, parents, and caregivers of the appropriate dosing for children (Table 1) and awareness of other products that contain acetaminophen (Table 2).

Table 2

Over-the-Counter and Prescription Drugs That Contain Acetaminophen*	
Anacin [®] -3	Lortab [®] 5/500
Anacin [®] -3 Extra Strength	Lortab [®] 7.5/500
Aspirin Free Anacin [®]	Lortab [®] 10/500
Aspirin-Free Excedrin [®] Caplets	Midol [®] Menstrual Formula Maximum Strength Caplets
Bayer [®] Select Maximum Strength Headache pain Relief Formula	Midol [®] Menstrual Formula Maximum Strength Gelcaps
Benadryl [®] Severe Allergy and Sinus Headache Maximum Strength Caplets	Midol [®] PMS Maximum Strength Caplets
Darvocet-N [®] 50	Norco [®] 5/325
Darvocet-N [®] 100	Norco [®] 7.5/325
Excedrin P.M. [®] Caplets	Norco [®] 10/325
Excedrin P.M. [®] Geltabs	Oxycet [®]
Excedrin P.M. [®] Tablets	Percocet [®] 2.5/325
Excedrin [®] Caplets	Percocet [®] 5/325
Excedrin [®] Extra Strength Caplets	Percocet [®] 7.5/325
Excedrin [®] Extra Strength Tablets	Percocet [®] 7.5/500
Feverall [®] Junior Strength	Percocet [®] 10/325
Feverall [®] Sprinkle Caps Junior Strength	Percocet [®] 10/500
Feverall [®] Sprinkle Caps, Children's	Roxicet [®] Elixir
Feverall [®] , Children's	Roxicet [®] 5/325
Feverall [®] , Infant's	Roxicet [®] 5/500
Goody's [®] Fast Pain Relief Tablets	Sinutab [®] Sinus Medication Maximum Strength Without Drowsiness Tablets
Goody's [®] Headache Powders	Sudafed [®] Sinus and Headache Caplets
Goody's [®] Extra Strength Tablets	Sudafed [®] Sinus & Headache Maximum Strength Tablets
Lorcet [®] 10/650	Talacen [®]
Lorcet Plus [®]	Tylox [®]
Lorcet-HD [®]	Vicodin [®]
Lortab [®] Elixir	Wygesic [®]
Lortab [®] 2.5/500	

* The foregoing list should not be construed to be all inclusive.

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Current guidelines recommend emergency room referral under the following circumstances surrounding RSTI of acetaminophen:

- Patients under 6 years of age:
 - 200 mg/kg or more over a single 24-hour period, or
 - 150 mg/kg or more per 24-hour period for the preceding 48 hours, or
 - 100 mg/kg or more per 24-hour period for the preceding 72 hours or longer
- Patients 6 years of age or older:
 - 10 g or 200 mg/kg (whichever is lower) over a single 24-hour period
 - 6 g or 150 mg/kg (whichever is lower) per 24-hour period for the preceding 48 hours or longer
- For patients with conditions that may increase susceptibility to acetaminophen toxicity (i.e. alcoholism, malnutrition, isoniazid use)

Chronic or repeated-supratherapeutic ingestions of acetaminophen are often insidious, and, therefore, present the potential for misdiagnosis. Serum acetaminophen levels are essential for evaluating toxicity for acute exposures, but are not an accurate monitoring parameter for supratherapeutic exposures or for acute ingestions that present late for treatment. The ability to interpret the trends in hepatic enzymes becomes essential in such cases. [12]

Treatment

Interpretation of Laboratory Values

Following a recent acute single ingestion, the decision to treat potential hepatotoxicity with the antidote, acetylcysteine, is determined by interpretation of the serum acetaminophen level as plotted on the Rumack-Matthew nomogram. [13] An acetaminophen level obtained less than 4 hours post an acute ingestion is generally not considered accurate, because the medication is still in absorption and distribution phases. Moreover, a serum level obtained greater than 24 hours after the ingestion cannot be accurately interpreted and is often misinterpreted as being subtoxic or even therapeutic. The most reliable levels are obtained 4-12 hours after an acute ingestion. It is also important to note that the nomogram is not useful for accurately evaluating toxicity in patients with chronic or repeated acetaminophen ingestions. [12, 14]

A reliable monitoring parameter for late or chronic acetaminophen toxicity involves following the trend of the hepatic enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), to monitor the degree of hepatic injury, as well as the PT and INR. Aminotransferase levels may begin to increase as early as 8 hours, but typically become elevated within 24-36 hours after a toxic acute ingestion of acetaminophen. Unlike a large acute ingestion, patients that ingest smaller multiple doses over a period of hours or days are likely to present with elevated aminotransferase levels. [12]

Decontamination

Though generally not helpful for chronic ingestions, effective gastrointestinal decontamination may obviate the need for further treatment and extended hospital admission for the patient that is discovered soon after an acute ingestion of acetaminophen. [15] Acetaminophen usually absorbs very quickly, therefore lavage is typically not very effective in preventing systemic absorption. Furthermore, the time it takes to perform lavage delays the administration of activated charcoal. Activated charcoal effectively adsorbs acetaminophen and can be administered to rapidly prevent systemic absorption of the drug. The use of activated charcoal alone has been shown to be as effective as the combination of lavage and charcoal; however, the activated charcoal is significantly less effective when given 2 hours post ingestion of acetaminophen versus 1 hour post. [16] This emphasizes the importance of early intervention with gastrointestinal decontamination. However, some published data provides evidence that suggests some efficacy of administering activated charcoal more than four hours after an acetaminophen overdose, and thus could offer benefit for late-presenting acute or supratherapeutic cases. [17]

Antidotal Therapy

The agent of choice for the treatment of acetaminophen overdose is N-acetylcysteine. As a substitute for glutathione, N-acetylcysteine binds directly to the toxic metabolite, NAPQI. Clear evidence states that treatment with acetylcysteine administered within 8 hours of ingestion is superior to treatment started beyond 8 hours. However, published data indicates that acetylcysteine may offer benefit if initiated between 15 - 24 hours after the time of ingestion. [18, 19] Currently, both the oral and intravenous routes are FDA approved. The most common protocol used in the U.S. for prevention of acetaminophen-induced hepatotoxicity is the 72-hour oral N-acetylcysteine protocol. The 21-hour intravenous N-acetylcysteine protocol is currently used in the U. S. as well. [9]

Oral N-acetylcysteine

An extemporaneous solution using inhaled N-acetylcysteine is prepared and administered orally according to a 72-hour protocol as follows:

Loading Dose: Give a single dose 140 mg/kg as a five percent (5%) solution in water, juice or soda.

Maintenance Doses: 4 hours after the loading dose, give doses of 70 mg/kg as a five percent (5%) solution in water, juice or soda every 4 hours, for 17 doses. [9]

Emesis during the administration of the oral regimen often develops due to the unpleasant taste and odor of the antidote. General recommendations to address this issue include administering each dose via nasogastric tube and antiemetic prophylaxis with metoclopramide or ondansetron. [20, 21] Emesis that persists in spite of these efforts should prompt the clinician to consider the intravenous option.

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Intravenous N-acetylcysteine

Though the practice is not FDA approved, intravenous use of the inhaled N-acetylcysteine has been administered due to a lack of an approved intravenous formulation. An FDA approved intravenous formulation of N-acetylcysteine is currently available under the trade name of Acetadote®. Though rare, anaphylactic reactions have occurred following the administration of intravenous N-acetylcysteine.

The 21-hour I.V. N-acetylcysteine Protocol for adult administration using the FDA approved intravenous formulation is as follows:

Loading Dose:	150 mg/kg in 200 mL 5% Dextrose infused intravenously over 60 minutes
Second Dose:	50 mg/kg in 500 mL 5% Dextrose infused intravenously over 4 hours
Third Dose:	100 mg/kg in 1000 mL 5% Dextrose infused intravenously over 16 hours

Though the calculations for dosing are the same as the above protocol, parenteral volumes must be appropriately adjusted for pediatric administration to prevent complication associated with hyponatremia. (See manufacturer recommendations). [19]

Special Consideration for Acute Ingestions

- A serum acetaminophen level should be drawn 4 hours after ingestion or as soon as possible. If the level plotted on the Rumack-Matthew nomogram crosses above the "treatment" line the patient is at risk for hepatotoxicity and should receive the full course of the antidote, N-acetylcysteine therapy as indicated.
- If a patient arrives 8 hours or more post ingestion, the N-acetylcysteine should be started until the serum level results indicate whether or not it should be continued.
- Patients that present 24 hours or more after ingestion should receive N-acetylcysteine if they have a measurable acetaminophen level or other evidence of hepatotoxicity.
- Patients who develop hepatotoxicity should receive N-acetylcysteine until hepatotoxicity improves. [9]

Special Considerations for Repeated-Supratherapeutic Ingestions

- Patients are at an increased risk of hepatotoxicity with chronic acetaminophen ingestions. N-acetylcysteine should be administered for any evidence of hepatotoxicity or for an acetaminophen level of greater than 10 mcg/mL upon presentation.
- The Rumack-Matthew nomogram cannot be used for chronic ingestions.
- N-acetylcysteine should be administered until hepatic enzymes are near normal and the acetaminophen level is undetectable; many clinicians recommend N-acetylcysteine for at least 24 - 36 hours from the last time of ingestion. Discontinue if hepatic enzymes remain normal and the acetaminophen level is undetectable.

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Prognosis

If a patient is at risk for developing acetaminophen toxicity and begins N-acetylcysteine prior to the onset of symptoms, then the patient has an excellent chance of survival. Of course, this is dependent upon early detection of the risk with a serum acetaminophen level accurately plotted on the nomogram indicating antidotal therapy is necessary. An incidence and outcome study that observed the frequency of acetaminophen overdose-related emergency department cases determined that a group of patients whose risk could not be estimated using the Rumack-Matthew nomogram had the poorest outcome. These atypical presenters represented 44% of the hospitalized patients and 83% of those who suffered hepatic injury. [22] Those patients with greatest chance of dying without a liver transplant present with a pH < 7.3, or with a combination of creatinine > 3.3mg/dL, PT > 100 seconds, and grade III or IV encephalopathy. Patients that meet these criteria are identified to be placed on the "super-urgent" transplant list. [23, 24] Patients with repeated-supratherapeutic ingestions or late presenters of acute overdose are at the greatest risk of hepatic injury and death. Early recognition using prognostic markers and patient education may help prevent many of these serious cases.

Conclusion

Acetaminophen had proven to be a safe and effective antipyretic/analgesic when used as recommended. However, because of the multitude of preparations, it is necessary that health care providers and patients be familiar with appropriate acetaminophen dosing. The Food and Drug Administration is currently proposing to make the warnings on over-the-counter analgesics clearer and stricter. The proposed regulations would require manufacturers to display on product packaging the safety information in a consistent manner. For example, acetaminophen packaging would contain the warning about liver damage, and product labels would have generic as well as the brand name of the product visible. Education to patients regarding the indication for their medication, appropriate use, and what is in the preparation they are taking is essential to minimize harm to patients.