DRUG SAFETY

Acetaminophen: Is Too Much of a Good Thing Too Much?

Jason H. Goodchild, DMD; and Mark Donaldson, BSP, ACPR, PharmD

Abstract: Acetaminophen is a popular, universally used, over-the-counter pain medication contained in more than 600 different products and available in a plethora of dosage forms. Acetaminophen is an important adjunct to manage postoperative dental pain in combination with a nonsteroidal anti-inflammatory drug such as ibuprofen. For the treatment of more severe pain, acetaminophen is often formulated with non-opioid and opioid agents. Because of the accessibility of acetaminophen and its widespread use, dental practitioners need to be cognizant of any significant safety concerns that may be associated with this drug, including acetaminophen toxicity. This article discusses the history of acetaminophen, its pharmacology, metabolism, and toxicity, as well as strategies to help address some of the potential safety issues with this medication, including unintentional overdosing.

LEARNING OBJECTIVES

- Discuss the history and development of acetaminophen as an over-the-counter pain medication
- Describe concerns that clinicians should be aware of regarding acetaminophen toxicity
- Identify recommendations for keeping the use of acetaminophen safe when managing postoperative dental pain

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Acetaminophen is one of the most universal over-the-counter (OTC) medications used to treat pain and fever, and the most common drug ingredient in the United States.[1-5] Fifty-two million consumers (approximately 23% of all adults in the United States) use an acetaminophen-containing product to manage fever and mild to moderate acute or chronic pain of headaches, migraine headaches, toothaches, menstrual cramps, and osteoarthritis.[6-10] Acetaminophen is also the drug of choice for pregnant and lactating women to treat mild pain and for children with fevers.[11-17]

More than 600 different products contain acetaminophen, and it is available in a plethora of dosage forms: capsules, chewable tablets, effervescent tablets, elixirs, extended-release tablets, suppositories, and regular oral tablets. In many countries purchases of acetaminophen-containing products are not restricted to pharmacies, and sales are increasing worldwide.[18] For the treatment of more severe pain, acetaminophen is often formulated with non-opioid and opioid agents such as ibuprofen, codeine, hydrocodone, oxycodone, and tramadol; acetaminophen and opioid-containing products are available by prescription only. Given the accessibility of acetaminophen and its widespread use, should there be any significant safety concerns within dentistry?

History

Some of the earliest remedies to treat fevers (antipyretic compounds) were known to be contained in white willow and cinchona bark.[19] These chemicals were known as salicins (which were the precursors of aspirin) and quinine (an anti-malarial drug, which also has anti-fever activity). The burgeoning science of pharmacognosy, however, led to the over-harvesting of many of these natural sources, and scientists began synthesizing new antipyretic agents in the laboratory, most notably acetanilide in 1886 and phenacetin the following year.[20]

Harmon Morse is credited with the production of acetaminophen in 1887, when he accidently prepared the drug by combining paranitrophenol, instead of analine, with glacial acetic acid and tin.[21] The discovery was made after the incorrect medicine, N-acetyl-para-aminophenol (acetaminophen or paracetamol) and not acetanilide, was given to a patient, yet his fever was still reduced. This new antipyretic, however, received very little interest until the 1940s when scientists rediscovered acetaminophen as the major

metabolite of phenacetin and acetanilide.[15-17] These findings were significant as phenacetin was associated with nephrotoxicity and acetanilide was found to cause methemoglobinemia, yet the analgesic and antipyretic effects of both of these medications were due to their active metabolite acetaminophen, which did not have either of these toxic effects.[16]

While the US Food and Drug Administration (FDA) first issued a patent for acetaminophen in 1951, McNeil Laboratories did not begin actively marketing the drug under the brand name Tylenol Children's Elixir® until 1955 as a fever and pain reliever for children.[6] A year later it was introduced in the United Kingdom as Panadol® where it is more frequently referred to as paracetamol. Sales of aspirin began to drop in the 1970s and 1980s due to safety concerns in children and certain adult populations, while phenacetin was withdrawn from the US market in 1983 due to unacceptable levels of interstitial nephritis in patients and potential risks of tumorigenicity. Both of these events led to the increased popularity and use of acetaminophen, and with expiration of the FDA patent in 1984 many generic versions and formulations of Tylenol® were produced and currently exist.

Pharmacology

Acetaminophen is thought to act within the central nervous system inhibiting central cyclooxygenase (COX) activity, an enzyme involved in prostaglandin synthesis, resulting in an increased pain threshold. Prostaglandins facilitate the inflammatory response responsible for inflammation, pain, and fever. Specifically, acetaminophen inhibits both central isoforms of the COX enzyme (COX-1 and COX-2) but does not inhibit prostaglandin synthesis in peripheral tissues. This explains acetaminophen's lack of peripheral anti-inflammatory effects.[22,23] However, while acetaminophen's exact mechanism of action is still unknown, investigators believe it may involve a specific interaction with a unique COX isozyme, or it may be by inhibition of nitric oxide synthesis or serotonergic pathways, or through an active metabolite influencing cannabinoid receptors.[22,24] The mechanism of action may also involve a combination of all of these routes.

The usual adult dose of acetaminophen is 325 mg to 650 mg every 4 to 6 hours, as needed for the treatment of mild pain. While 1000 mg up to four times per day can be administered, it is important not to exceed 1000 mg per dose or 4000 mg in a 24-hour period.[6,22] A statement from the American Dental Association (ADA) House of Delegates states that, "Dentists should consider nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line therapy for acute pain management, and for situations in which NSAIDs alone are not effective, the combination of a NSAID with acetaminophen is recommended."[25,26] This closely aligns with the prescribing mnemonic "2-4-24" first published in 2010 to help prescribers remember the prescription of choice for acute postoperative orofacial pain.[27] This mnemonic refers to a combination of acetaminophen 650 mg to 1000 mg and ibuprofen 600 mg to be administered every 6 hours for 24 hours: "two drugs, in four doses, for 24 hours." A more recent publication further suggests that the anticipated pain level for the patient can also help determine the best postoperative analgesic prescribing regimen.[28]

> **Specifically, acetaminophen inhibits both central isoforms of the COX enzyme (COX-1 and COX-2) but does not inhibit prostaglandin synthesis in peripheral tissues.**

While Advil Dual Action® may seem like an ideal postoperative analgesia strategy to improve patient compliance by minimizing the potential pill burden to the patient, there may be shortcomings related to this combination product to consider. Most importantly, the target doses of the "2-4-24" strategy (acetaminophen 650 mg and ibuprofen 600 mg per dose) are impossible to achieve when using the fixed dose tablets of Advil Dual Action (acetaminophen 250 mg and ibuprofen 125 mg per dose). Secondly, if patients attempt to match the optimal analgesic dose of ibuprofen 600 mg using this OTC pain medication, they will greatly exceed the recommended maximum dose of acetaminophen, which is known to have serious health implications, including potential liver toxicity and mortality.

Metabolism and Toxicity

Acetaminophen has an elimination half-life of 2 to 3 hours in healthy adult patients and is renally excreted as the sulfate metabolite (25% to 35%) and the glucuronide conjugate (40% to 65%);

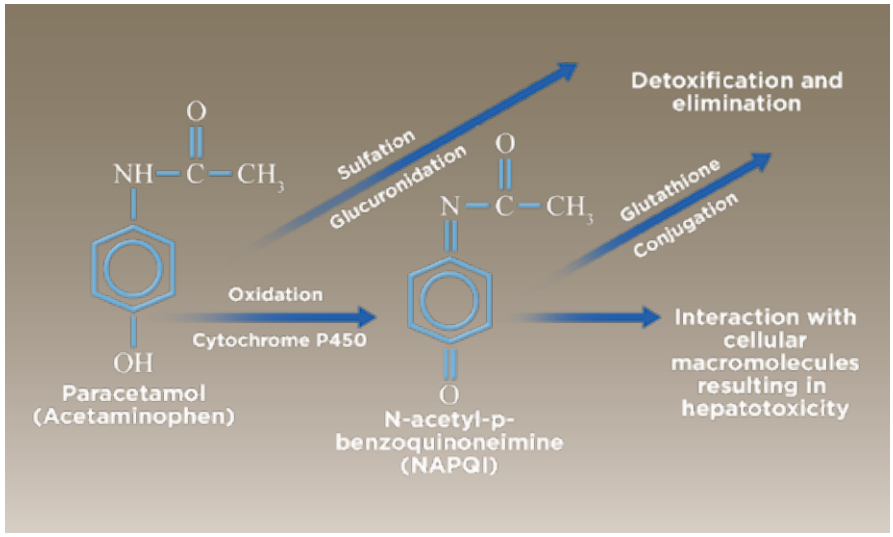

Fig 1. Acetaminophen metabolism.

less than 5% is excreted as unchanged drug.[6,22] Acetaminophen is metabolized in the liver via three separate pathways: glucuronidation, sulfation, and cytochrome P450 (CYP450) oxidation (Figure 1). Glucuronidation and sulfation are the primary routes of metabolism in detoxifying and eliminating the drug from the body, while a minor amount of acetaminophen undergoes oxidative metabolism by isoenzyme CYP2E1 creating the hepatotoxic metabolite, N-acetyl-p-benzoquinoneimine (NAPQI). NAPQI is rapidly conjugated with glutathione to inert metabolites when acetaminophen is administered at therapeutic doses.[6,22,24,29,30] Repeated therapeutic doses or supratherapeutic doses of acetaminophen, fasting, and alcoholism can deplete glutathione stores, however, resulting in hepatotoxicity due to increased concentrations of NAPQI in the blood.[22,30]

Regulations

The hepatotoxic effects of NAPQIs have been well-documented and are the most common cause of acetaminophen toxicity leading to acute liver failure in both the United States and the United Kingdom.[31,32] In a combined 5-year study from 22 specialty medical

TABLE 1

Issues Addressed by the FDA Analgesic Advisory Committee Concerning Acetaminophen Toxicity

Question	Approved/Not Approved
Reduce current dosage strengths for OTC products: maximum total daily dose, maximum adult single dose, maximum strength? • Maximum dose per day: less than 4 g, exact amount unspecified. • Maximum single dose: 650 mg (2 x 325 mg).	Approved
If the above is approved, should 500 mg tablet, 1000 mg, and/or 4 g/day dosing be prescription only? • Maximum dose of 500 mg x 2 should be prescription only.	Approved
Establish pack size limits for OTC acetaminophen products? • Pack size limits?	Not approved
Eliminate non-prescription combination products (eg, Nyquil®, Dayquil®)? • Eliminate these products?	Not approved
Limit formulations of liquids to only one concentration (this has to do with pediatric dosing)? • Do you recommend that only one non-prescription concentration of liquid be available?	Approved
Eliminate prescription combination products (opioid/acetaminophen compounds)? • Do you recommend eliminating the prescription combination products?	Approved
If not eliminated, should prescription combinations be sold in "unit of use" packaging or with additional warning labels? • Do you recommend "unit of use" packaging? • Do you recommend box warning?	Approved

OTC = over-the-counter

TABLE 2

Examples of Acetaminophen/Opioid Combination Products Before and After FDA Decision to Limit Amount of Acetaminophen in These Products to 325 mg Per Tablet, Capsule, or Other Dosage Unit

Product Name	Amount of Acetaminophen Per Unit Before 2011	Amount of Acetaminophen Per Unit After 2011
Tylenol® Regular Strength	325 mg	325 mg
Tylenol® Extra Strength	500 mg	500 mg
Vicodin®	500 mg / 750 mg	325 mg
Lortab®	500 mg	325 mg
Lorcet®	650 mg	325 mg
Percocet®	325 mg / 500 mg	325 mg
Tylenol® #3	300 mg	300 mg

centers in the United States, acetaminophen-induced liver injury led all causes of acute hepatic failure.[31] Almost half of the reported cases were due to unintentional overdoses where acetaminophen toxicity occurred as the result of acute overdose or chronic excessive dosing.[31] Early nonspecific symptoms of acetaminophen-induced hepatotoxicity include abdominal pain, malaise, nausea/vomiting, and anorexia, which may progress to more severe signs such as jaundice, hepatic encephalopathy, and hepatic necrosis.[7,33]

Between 1998 and 2003, acetaminophen-related acute liver failure cases increased from 28% of all acute liver failure cases in the United States to 51%.[31] From 2000 to 2004, 86% of the 1,600 cases of acute liver failure in the United States were due to unintentional or intentional acetaminophen overdoses.[34] The mounting evidence linking acute liver failure with acetaminophen prompted the FDA to assemble its Analgesic Advisory Committee in 2009 to vote on seven specific questions (Table 1).[35] This meeting resulted in proposed strategies for acetaminophen dose reduction in order to decrease morbidity and mortality: decrease the maximum single dose from 1000 mg to 650 mg, reduce the maximum daily dose from 4000 mg to 3250 mg, reclassify 500 mg strength tablets to prescription status, and eliminate prescription and nonprescription acetaminophen-combination drugs.[35]

So far the FDA has instituted only one of the proposed strategies to help address some of the safety concerns with acetaminophen: limit the amount of acetaminophen in combination products to 325 mg per capsule, tablet, or other dosage units (Table 2).[35-38] This is particularly interesting as Johnson & Johnson, without being regulated by the FDA to do so, modified the labeling of Tylenol® in 2012 to recommend a maximum adult daily dose of just 3000 mg.[39] A timeline of all FDA acetaminophen actions is shown in Figure 2.

In 2021, a group of experts from Australia, Brazil, Canada, Europe, Israel, Scotland, United Kingdom, and United States published a consensus statement in *Nature Reviews Endocrinology* highlighting the potential risks of acetaminophen use during pregnancy.[40] Based on the results of 29 studies investigating the use of acetaminophen, 26 found causative evidence of birth defects, including increased risks of some reproductive, urogenital, and neurodevelopmental disorders. These effects are dependent on the timing of exposure in relation to specific developmental processes and duration as well as dose. Interestingly, the article does not call for a ban on using acetaminophen during pregnancy, but the experts urge both patients and healthcare providers to regard acetaminophen with caution. Oral healthcare providers should be reminded that NSAIDs such as ibuprofen as well as aspirin are not suitable alternatives as they carry an even higher risk of fetotoxicity compared to acetaminophen when administered during pregnancy. The consensus statement also included recommendations for US and European regulatory agencies (ie, the FDA and the European Medicines Agency) to conduct new safety reviews of acetaminophen and update recommendations accordingly. Additional recommendations that providers can give to patients to help keep the use of acetaminophen safe are as follows:

> **In a combined 5-year study from 22 specialty medical centers in the United States, acetaminophen-induced liver injury led all causes of acute hepatic failure.**

- Patients should know the milligrams of acetaminophen in their tablets/capsules. In OTC acetaminophen products, each pill may contain 325 mg or 500 mg of the drug. Extra caution needs to be used when taking 500 mg or 650 mg pills.

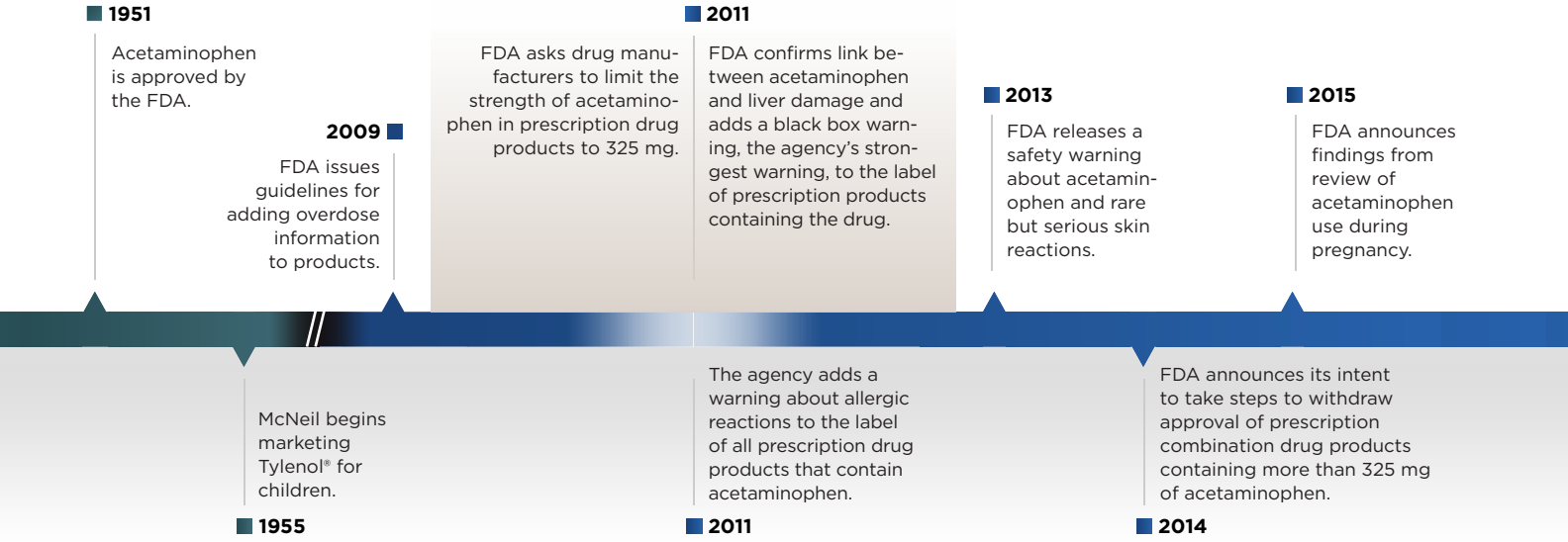

Fig 2. Timeline of all FDA acetaminophen actions taken in the United States.

- Patients should beware of "shotgun" preparations: medications which contain multiple ingredients that include acetaminophen. They should review the labeled ingredients of all OTC as well as prescription products (including cough, cold, and flu remedies and analgesics).
- Alcohol intake should be minimal, if done at all. Studies show that people who drink more than three alcohol-containing drinks a day and take acetaminophen are at increased risk of developing hepatotoxicity.[41,42] Drinking alcohol causes the liver to convert more of the ingested acetaminophen into toxic byproducts (NAPQI).
- Pregnant or breastfeeding patients should avoid ingesting any medications without first consulting their physician. Increasing experimental and epidemiological research suggests that prenatal exposure to acetaminophen might alter fetal development.[40]
- Patients should ask their doctor or pharmacist if any of their medications could interact with acetaminophen, although this is rare. (Alcohol is most noteworthy.)
- Patients need to adhere to recommended doses (at present this should be less than 4000 mg a day of acetaminophen from all sources, and less for smaller individuals). When taking acetaminophen, overcome any urge to exceed recommended doses, as most cases of acetaminophen toxicity are unintentional.

Conclusions

Last year, 2021, marked the 70th anniversary of the approval of acetaminophen for use in the United States. It continues to be a popular choice for treating pain and fever, including for special populations such as pregnant and lactating women experiencing mild pain and children with fevers. Acetaminophen is also an important adjunct, endorsed by the ADA, to manage postoperative dental pain in combination with a NSAID such as ibuprofen. Despite the widespread availability and general safe use, acetaminophen toxicity continues to be the most common cause of acute liver failure as the result of chronic excessive dosing or acute overdose, which in most cases is unintentional. Also, new epidemiological and experimental research suggests that prenatal exposure to the drug can alter fetal development, increasing the risks of some reproductive, urogenital, and neurodevelopmental disorders. The general public as well as all healthcare professionals need to remember that sometimes too much of a good thing is too much.

ABOUT THE AUTHORS

Jason H. Goodchild, DMD
Vice President of Clinical Affairs, Premier Dental Products Co., Plymouth Meeting, Pennsylvania; Associate Clinical Professor, Department of Oral and Maxillofacial Surgery, Creighton University School of Dentistry, Omaha, Nebraska; Adjunct Assistant Professor, Division of Oral Diagnosis, Department of Diagnostic Sciences, Rutgers School of Dental Medicine, New Brunswick, New Jersey

Mark Donaldson, BSP, ACPR, PharmD
Associate Principal, Vizient Pharmacy Advisory Solutions, Irving, Texas; Clinical Professor, School of Pharmacy, University of Montana, Missoula, Montana; Clinical Assistant Professor, School of Dentistry, Oregon Health & Sciences University, Portland, Oregon; Adjunct Professor, Faculty of Dentistry, University of British Columbia, Vancouver, British Columbia; Fellow, American Society of Health-System Pharmacists; Fellow, American College of Healthcare Executives®

Queries to the author regarding this course may be submitted to authorqueries@aegiscomm.com.

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QUIZ

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1. **A widely used over-the-counter pain medication, acetaminophen is contained in how many different products?**
   A. about 50
   B. 100 to 150
   C. 250 to 300
   D. more than 600

2. **The US Food and Drug Administration (FDA) first issued a patent for acetaminophen in:**
   A. 1887.
   B. 1951.
   C. the 1970s.
   D. 1983.

3. **Acetaminophen is thought to act within the central nervous system inhibiting:**
   A. cytochrome P450 (CYP450) oxidation.
   B. central cyclooxygenase (COX) activity.
   C. interaction with cellular macromolecules.
   D. N-acetyl-p-benzoquinoneimine (NAPQI) conjugation.

4. **The usual adult dose of acetaminophen, as needed for treatment of mild pain, is:**
   A. 125 mg to 250 mg every 3 to 4 hours
   B. 325 mg to 650 mg every 4 to 6 hours.
   C. 700 mg to 850 mg every 4 to 6 hours.
   D. 1250 mg four times per day.

5. **The mnemonic "2-4-24" refers to a combination of acetaminophen 650–1000 mg and ibuprofen 600 mg to be administered every 6 hours for 24 hours, thus:**
   A. "two drugs, in four doses, for 24 hours."
   B. "two drugs, in two doses, for 12 hours."
   C. "three drugs, in six doses, for 24 hours."
   D. "four drugs, in two doses, for 48 hours."

6. **Acetaminophen is metabolized in the liver via which of the following pathways?**
   A. glucuronidation
   B. sulfation
   C. CYP450 oxidation
   D. All of the above

7. **Repeated therapeutic or supratherapeutic doses of acetaminophen, fasting, and alcoholism can deplete glutathione stores, resulting in:**
   A. birth defects.
   B. hyperlipidemia.
   C. hepatotoxicity.
   D. All of the above

8. **From 2000 to 2004, 86% of acute liver failure cases in the United States were due to:**
   A. intentional opioid overdoses.
   B. unintentional ibuprofen overdoses.
   C. unintentional or intentional acetaminophen overdoses.
   D. unintentional phenacetin overdoses.

9. **To address safety concerns, the FDA has limited the amount of acetaminophen in combination products to:**
   A. 275 mg per capsule or other dosage unit.
   B. 300 mg per capsule or other dosage unit.
   C. 325 mg per capsule or other dosage unit.
   D. 375 mg per capsule or other dosage unit.

10. **To maintain safety, patients should be aware of "shotgun" preparations, which are medications that:**
    A. contain multiple ingredients that include acetaminophen.
    B. contain 500 mg acetaminophen pills.
    C. interact with acetaminophen.
    D. include opioid agents.

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CVV Code ☐☐☐

Signature _____ **Date** _____

(PLEASE PRINT CLEARLY)

LAST 4 DIGITS OF SSN ☐☐☐☐

ADA NUMBER ☐☐☐☐☐☐☐☐☐

AGD NUMBER ☐☐☐☐☐☐

Month/Day of Birth ___ ___ /___ ___
(Example: January 23 is 01/23, no year.)

NAME _____

ADDRESS _____

CITY _____

STATE _____ **ZIP** _____

E-MAIL ADDRESS _____

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PROGRAM EVALUATION

Please circle your level of agreement with the following statements.
(4 = Strongly Agree; 0 = Strongly Disagree)

1. Clarity of objectives — 4 3 2 1 0
2. Usefulness of the content — 4 3 2 1 0
3. Benefit to your clinical practice — 4 3 2 1 0
4. Usefulness of the references — 4 3 2 1 0
5. Quality of the written presentation — 4 3 2 1 0
6. Quality of the illustrations — 4 3 2 1 0
7. Clarity of review questions — 4 3 2 1 0
8. Relevance of review questions — 4 3 2 1 0
9. Did this lesson achieve its educational objectives? — Yes No
10. Did this article present new information? — Yes No
11. How much time did it take you to complete this lesson? _____ min