

Science Brief on Acetaminophen and Liver Injury

ADA Council on Scientific Affairs

THE ISSUE

How would proposed restrictions on acetaminophen, as recommended by an FDA advisory panel, impact dentistry?

BACKGROUND

In June 2009, a joint advisory panel to the U.S. Food and Drug Administration (FDA) approved a preliminary recommendation in favor of eliminating prescription acetaminophen combination products, such as Vicodin® or Lortab® (a combination of acetaminophen and hydrocodone) and Percocet® (a combination of acetaminophen and oxycodone).¹ This panel recommendation was purely advisory to the FDA, and as of April 2010, it is under evaluation by the FDA for further action and/or final ruling(s).

The advisory panel also issued the following recommendations for the FDA's consideration:

- reducing the maximum daily adult dose of acetaminophen products to less than 4000 milligrams per day (note: new maximum daily dose was not specified);
- switching the current maximum single dose of acetaminophen for adults (1000 mg, or two 500 mg tablets) to prescription-only status;
- lowering the maximum single adult dose of acetaminophen to 650 mg in over-the-counter medications (e.g., Tylenol, Excedrin);
- requiring a black-box warning on any acetaminophen combination product that remains available by prescription; and
- proposing that only one standard acetaminophen concentration be made available to the public (including pediatric patients) in over-the-counter liquid formulations (e.g., Theraflu).

These recommendations were adopted at a two-day joint session of the FDA Drug Safety and Risk Management Advisory Committee, the Anesthetic and Life Support Drugs Advisory Committee; and the Nonprescription Drugs Advisory Committee. The meeting was held in June 2009 to consider several suggested options for addressing the persistent public health issue of acetaminophen-related liver injury. In recent years, the FDA has conducted several safety reviews of the benefits and risks of acetaminophen products,²⁻⁴ and it plans to review the advisory panel's recommendations and other perspectives presented at the June 2009 panel meeting. A final ruling is expected in the near future.

This Science Brief presents an overview of recommended safety controls to promote the appropriate use of acetaminophen-containing medications by patients for managing pain of dental origin, and to reduce the incidence of liver injury from acetaminophen overdose, particularly in patients at elevated risk for adverse events. The Brief is intended to serve as a resource in advance of any final FDA action on the June 2009 advisory panel recommendations, which could have significant implications for dentists, who commonly recommend and/or prescribe acetaminophen-containing medications for dental pain management.⁵⁻⁷

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* Inclusion of a product/brand name in this Science Brief is not intended as an endorsement of any specific product or medication.

ACETAMINOPHEN OVERDOSE AND LIVER TOXICITY

Acetaminophen, or N-acetyl-para-aminophenol, is one of the most widely utilized medications in the United States,⁸ with over 24 billion doses sold (prescription and non-prescription) in 2008.⁹ Acetaminophen is an effective analgesic and antipyretic (fever reducer) available in many over-the-counter (OTC) products, including headache treatments, sleep aids, cough suppressants and cold formulations. Unlike non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen, acetaminophen does not exert a peripheral anti-inflammatory effect.

When used as directed, acetaminophen-containing products have an extensive history of patient safety in prescription formulations and OTC products, such as Tylenol, Excedrin and other brands.¹⁰⁻¹² Dentists and physicians have long relied on acetaminophen as a valuable primary or alternative analgesic, including its availability in prescription combination products with opioids (e.g., hydrocodone). The use of 1,000 mg of acetaminophen every six hours, or 650 mg every four hours, falls at or near the current maximum daily adult dosage (4,000 mg/day). Systematic reviews indicate that short-term use of acetaminophen at standard doses provides effective pain management for adult patients.^{12,13}

However, despite an extensive record of safety, acetaminophen also holds considerable potential for adverse health consequences when individuals exceed the recommended maximum daily dose of 4000 mg per day, particularly for several days or longer, although very high single doses are also harmful. Acetaminophen overdose has been identified as the primary cause of acute liver failure in the United States,^{14,15} and it is commonly linked with simultaneous use of multiple acetaminophen-containing products (prescription or OTC). Excessive use of acetaminophen, both intentional and unintentional, is associated with nearly 56,000 emergency room visits and over 400 fatalities each year.¹⁶ Individuals who consume three or more alcoholic beverages per day are also considered more susceptible to unintentional acetaminophen overdose.^{4,14,17}

Patients are often unaware that overuse of acetaminophen-containing medications is a primary cause of acute liver failure, and that they can quickly reach and exceed the maximum daily dose using OTC and prescription products.^{18,19} Those who use multiple products, like cold medications and pain relievers, also may not realize that each product contains acetaminophen. Many individuals also use single-ingredient, OTC acetaminophen to relieve acute pain such as toothache, which is a common indication for use for OTC acetaminophen products.²⁰ These are important considerations for practicing dentists, who help patients manage acute pain in the orofacial region. Importantly, cases of acetaminophen overdose have been reported in the U.S. and Europe in individuals who were self-medicating their dental pain with over-the-counter products.²¹⁻²³ In a 2008 case report, a 19-year-old college student died after taking excessive amounts of OTC acetaminophen for several days.²⁴ Presenters at the June 2009 FDA meeting also cited the case of a 33-year-old man who received emergency room treatment after taking approximately 12 grams of OTC acetaminophen tablets daily for 2-3 days to relieve pain from an impacted wisdom tooth.²⁵

USE OF ACETAMINOPHEN FOR DENTAL PAIN MANAGEMENT

Dentists routinely manage acute pain of dental origin, and analgesic medications are often prescribed to relieve dental pain.²⁶ Acute pain is commonly associated with inflammation of oral and/or dental tissues, and patients with pain may begin OTC acetaminophen treatment before visiting their dentist. For these reasons, effective management of pre-procedural and/or post-operative pain is an integral component of dental practice.

Fortunately, most oral/dental pain falls within the mild-to-moderate range, and patients may only need simple analgesics, including acetaminophen, for 1 to 3 days following an invasive procedure. Acetaminophen (sometimes abbreviated APAP) is indicated for the treatment of mild-to-moderate dental pain, and is generally considered safe when used appropriately.¹²

Depending on the patient's individual circumstances, several options are available for over-the-counter, post-operative pain management (e.g., 650-1000 mg acetaminophen) or non-steroidal anti-inflammatory drugs (NSAIDs), such as 400 mg ibuprofen or 440 mg naproxen sodium, both of which are documented to control oral surgical pain effectively.²⁷ Several studies have demonstrated the effectiveness of 1000 mg acetaminophen for treatment of oral surgery pain following simple dental extraction, periodontal surgery, or impacted third molar surgery.^{28,29}

For cases of moderate-to-severe dental pain, acetaminophen is also utilized in combination products with opioids, such as codeine, oxycodone (e.g., Percocet), or hydrocodone (e.g., Vicodin, Lortab) in patients who cannot take NSAIDs.³⁰

SAFETY CONTROLS AND PRESCRIBING CONSIDERATIONS

To promote patient safety and wellness, the following recommendations are provided for dentists to consider when prescribing acetaminophen-containing medications for the management of dental pain:

- **Obtain a comprehensive health history:** Dental clinicians should take a detailed medical history for all patients, remain informed of all changes to a patient's health history and medication use, and consult with the patient's physician as appropriate. In assessing a patient's health history, conditions that may affect an individual's ability to metabolize medications should be carefully evaluated. For acetaminophen, existing liver damage is one such consideration since it is the primary site of the drug's metabolism.
- **Short-term prescribing of acetaminophen-containing analgesics:** Following invasive dental/oral surgical procedures, acetaminophen-containing medications are usually prescribed for short durations of time (e.g., one to three days). For this reason, instances of acetaminophen-related liver toxicity in dental patients are rare, and significant pain reduction is commonly achieved after the first post-operative day.¹² Some dentists manage patients with chronic pain (e.g., myofascial, musculoskeletal, neurogenic). These patients should be cautioned to closely follow manufacturer or prescription directions, and to find out if any OTC medicine they plan to take in addition to their pain medication contains acetaminophen.
- **Understand that different brands of acetaminophen-opioid combinations, even with the same opioid, have different doses of acetaminophen added:** Dentist should be fully aware of the acetaminophen dose in a prescribed acetaminophen-opioid combination to determine the maximum daily dose of any specific acetaminophen-opioid combination. For example, several combination products that contain hydrocodone have variable acetaminophen dosages (e.g., Lortab 5/500, Lortab 7.5/500, Lortab 10/500, Norco 5/325, Vicodin 5/500, Vicodin 7.5/750, Vicodin HP 10/660). The maximum daily dose of combination opioid/acetaminophen products is based on the recommended maximum daily dose of acetaminophen (4000 mg). A common problem is writing a prescription for a hydrocodone 5 mg/acetaminophen 500 mg product as 1-2 T q4-6h for pain (i.e., 1 or 2 tablets every 4 to 6 hours), which may result in 12 tablets being taken in one day and a total daily acetaminophen dose of 6000 mg, well above the recommended daily dose for adults. If a hydrocodone 5 mg/acetaminophen 325 mg product is chosen, 12 tablets would provide a total daily acetaminophen dose of only 3900 mg, and below the recommended daily maximum.
- **Educate patients of the risks associated with unintentional acetaminophen overdose:** Every patient who is prescribed medication containing acetaminophen should be informed verbally that the medication being prescribed contains acetaminophen, and that it should not be combined with other OTC acetaminophen products. Patient education is essential because most are not aware that prescription analgesics, such as Vicodin or Percocet, contain acetaminophen as well.^{15,17,18} Clear,

concise communications with patients could include one or more of the following messages: “Follow directions carefully for all medications”; “Discontinue using more than one medication with acetaminophen (OTC and/or prescription)”; “Don’t presume over-the-counter medications are safe at any dose or duration of use”; “More is not necessarily ‘better’ with OTC medications.” If not contraindicated, NSAIDs (e.g., ibuprofen, naproxen sodium) may be added to an acetaminophen-opioid combination, rather than increasing the dose of acetaminophen.

- **Identify patient risk factors for adverse drug interactions with acetaminophen-containing medications:** Dentists should obtain a full history of each patient’s use of OTC and prescription medications containing acetaminophen, plus information on acetaminophen dosages and dose intervals. Acetaminophen-containing medications should not be recommended or prescribed for the following patients, unless with physician consultation:
 - Individuals who consume three or more alcoholic beverages per day;^{4,14,17}
 - Former chronic users of alcohol;³¹
 - Patients with active liver disease or past liver damage (also use with caution in patients with compromised liver function);
 - Patients with advanced kidney disease;³²
 - Patients who are malnourished or fasting;³³
 - Individuals taking warfarin (e.g., Coumadin®), if acetaminophen will be prescribed for more than a few days.

- **Encourage patients to avoid simultaneous use of over-the-counter acetaminophen-containing medications with prescription-only acetaminophen combination products (e.g., Vicodin, Lortab):** As prescribers, dentists should advise patients against taking excessive amounts of acetaminophen. Routine users of OTC pain medications should monitor their daily intake of acetaminophen from all sources (OTC and prescription). In particular, patients should be warned to avoid concurrent use of OTC products containing acetaminophen (e.g., Tylenol, Nyquil) and prescription opioid-acetaminophen combinations.

- **Advise patients of the availability of alternative analgesics with lower risks of liver injury:** Studies suggest that non-steroidal anti-inflammatory drugs, such as 400 mg ibuprofen, provide comparable or superior efficacy to opioid-acetaminophen combination products.^{27,34} Patients who can tolerate NSAIDs can be advised to use OTC medications such as ibuprofen or naproxen sodium for relief of mild to moderate pain. If prescription-level medications are indicated, dentists may recommend prescription-strength NSAIDs and/or other non-narcotic or narcotic analgesic medications. Due to regulation and the risk of drug diversion, many pharmacies do not stock some (or all) controlled drugs. Consult with local pharmacies regarding availability if necessary.

- **Caution patients about adverse events associated with narcotic-acetaminophen combination products:** Patients who take analgesics that combine opioids with acetaminophen (e.g., Vicodin, Percocet) may experience nausea, vomiting, itching or constipation as common side effects. While physiological effects (e.g., physical dependence and tolerance), as well as addictive behaviors, are exceedingly rare with short-term (1-3 days) use of opioids, long-term opioid therapy increases these risks. Opioid-acetaminophen combinations should not be prescribed to individuals with opioid intolerance or allergy, chronic respiratory disease, those who consume substantial quantities of alcohol (e.g., more than 3 beverages a day) or those with previous history of opioid abuse, without physician consultation. Also, narcotic analgesics (e.g., codeine, hydrocodone, oxycodone) may restrict or reduce salivary flow (xerostomia), which can contribute to oral manifestations.

ADDITIONAL CONSIDERATIONS

Given its strong record of safety and effectiveness, acetaminophen is commonly recommended as a first-line treatment for mild-to-moderate pain, and as a preferred analgesic for pregnant women, pediatric patients and the elderly.³⁵ Yet along with acetaminophen, an extensive body of pain research also supports conventional NSAIDs (e.g., ibuprofen) as effective analgesic treatments. According to earlier studies and the [Oxford League Table of Analgesic Efficacy](#) (a compilation of comparative scientific data on analgesics), NSAIDs can provide adequate control of moderate-to-severe pain, when compared with either acetaminophen-opioid combinations or acetaminophen alone.^{27,35} When appropriate, beginning NSAID therapy before invasive procedures may improve pain management, as can taking the medication “by the clock” initially, rather than “as needed.”

On the other hand, acetaminophen is an important short-term alternative to NSAIDs for individuals with risk factors for ischemic heart disease (e.g., recent bypass surgery, unstable angina or myocardial infarction, or ischemic cerebrovascular events). Specifically, in patients at risk for thromboembolism, the American Heart Association has emphasized the greater safety of acetaminophen, aspirin, and opioids, when compared to both non-selective and COX-2-selective NSAIDs.³⁶ One basis for this recommendation is that acetaminophen does not affect cyclooxygenases important for platelet function.

Patients allergic to NSAIDs, and those with gastric bleeding and/or gastrointestinal (GI) problems should not take NSAIDs (e.g., aspirin, ibuprofen) because of potential deleterious effects on the GI track (e.g., ulcers). NSAIDs increase the risk of kidney damage in patients who are volume-depleted or who have pre-existing renal disease. Pregnancy also contraindicates the use of NSAIDs. Opioid-acetaminophen analgesics are generally recommended for patients with GI problems if acetaminophen alone is insufficient for effective pain management. NSAIDs should be avoided in patients taking warfarin (e.g., Coumadin).

FDA FINAL RULING PENDING

Combination therapies are commonly used by dentists for the management of postoperative dental pain, and this form of analgesic intervention is currently under review by the FDA for potential elimination from the U.S. market.¹ If prescription combination products containing acetaminophen are eliminated, dentists could consider the following alternatives for postoperative pain management:

- In most pain control situations, ibuprofen at doses between 400-600 mg is considered effective.²⁷ If additional analgesia is required, oxycodone 5 mg may be added to ibuprofen 400 mg, as this has also been shown to provide effective pain relief.³⁷
- 400 mg of ibuprofen (e.g., Advil, Motrin) or 440 mg naproxen sodium are comparatively equivalent in efficacy or superior to opioid-acetaminophen combination products, such as Vicodin.²⁷

As a final consideration, dentists are encouraged to remain vigilant and monitor patients suspected of having initial symptoms of acetaminophen overdose, such as: nausea/vomiting, abdominal pain, jaundice, fatigue, skin rashes and/or itching of skin, and/or fluid retention.³⁸ When evaluating a patient’s full history of OTC and prescription medications, dentists could refer individuals suspected of potential overdosing of acetaminophen-opioid medications to their physician and/or pharmacist as appropriate.

CONCLUSIONS

The Council on Scientific Affairs recommends raising awareness among dental patients that many OTC products (e.g., cold medications, pain relievers) and prescription medications contain acetaminophen.

Patients should be fully informed of potential adverse events associated with excessive use of acetaminophen, particularly with the concurrent use of OTC acetaminophen products and prescription analgesic medications that combine acetaminophen with an opioid. Pending the issuance of updated FDA guidance on acetaminophen-containing medications, the Council's consensus is that the current scientific evidence supports the safety of acetaminophen-containing medications for short-term management of mild-to-moderate pain when used at appropriate dosages and dose intervals.^{12,13,29} If opioid-acetaminophen combination analgesics are eliminated from the marketplace, dentists may prescribe more NSAID medications or other single-agent narcotic or non-narcotic analgesic agents for dental pain management. Use of a single-agent opioid prescription medication with an OTC acetaminophen product may be considered for patients who are able to manage this option.

Finally, the Council supports the public health initiative to reduce the incidence of acetaminophen-induced liver injury, and recommends improved OTC and prescription product labeling for acetaminophen medications, along with enhanced public information about the hazards of acetaminophen overdose. For additional information on acetaminophen medications, dentists are encouraged to consult the following resources:

- the [ADA/PDR® Guide to Dental Therapeutics, Fifth Edition](#);
- [acetaminophen safety information from the U.S. Food and Drug Administration](#); and
- the ADA Center for Evidence-Based Dentistry's [database of systematic reviews on anesthesia, oral sedation and pain control](#).

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