Acetaminophen: Old Drug, New Issues

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Abstract

Introduction: The purpose of this review was to discuss new issues related to safety, labeling, dosing, and a better understanding of the analgesic effect of acetaminophen. **Methods:** The MEDLINE, Embase, Cochrane, and PubMed databases were searched. Additionally, the bibliography of all relevant articles and textbooks were manually searched. Two reviewers independently selected the relevant articles. **Results:** Concerns about acetaminophen overdose and related liver failure have led the US Food and Drug Administration to mandate new labeling on acetaminophen packaging. In addition, large-scale epidemiologic studies increasingly report evidence for second-generation adverse effects of acetaminophen. Prenatal exposure to acetaminophen is associated with neurodevelopmental and behavioral disorders. Recent studies also suggest that acetaminophen is a hormone disrupter (ie, it interferes with sex and thyroid hormone function essential for normal brain development) and thus may not be considered a safe drug during pregnancy. Finally, emerging evidence suggests that although the predominant mechanism by which acetaminophen exerts its therapeutic effect is by inhibition of cyclooxygenase, multiple other mechanisms also contribute to its analgesic effect. **Conclusions:** Available evidence suggests that indiscriminate usage of this drug is not warranted. and its administration to a pregnant patient should be considered with great caution. *(J Endod 2015;41:588–593)*

Key Words

Acetaminophen, mechanism of action, paracetamol, review, side effects

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Acetaminophen (also known as N-acetyl-p-aminophenol or APAP) or paracetamol (PARA) is 1 of the most popular analgesic and antipyretic agents in the United States (1). Because PARA is not widely recognized in the United States, in this article acetaminophen will be used. Acetaminophen is a member of the aniline family of analgesics, and it is the only such drug available in the United States.

A January 13, 2011, Food and Drug Administration (FDA) Drug Safety Communication states that "acetaminophen-containing prescription products are safe and effective when used as directed, though all medications carry some risks" (2). Indeed, during the past decade, acetaminophen has been identified as the leading cause of acute liver failure in the United States, and up to 50% of the cases are caused by an unintentional overdose (3–6). To address the issues surrounding acetaminophen toxicity, the FDA Center for Drug Evaluation and Research prepared an internal report that formed the basis for discussion at the 2009 advisory committee meeting to mandate new labeling on over-the-counter acetaminophen packaging (7). Subsequently, on January 13, 2011, confirming acetaminophen as a dose-dependent hepatotoxin, the FDA asked drug manufactures to limit the strength of acetaminophen in prescription drug products (eg, acetaminophen-opioid combinations) to 325 mg per tablet, capsule, or other dosage unit (2). On January 14, 2014, the FDA called on health care professionals to discontinue prescribing and dispensing prescription combination drug products with more than 325 mg acetaminophen (8). Ultimately, on March 26, 2014, the FDA and the pharmaceutical industry took action to protect consumers from the risk of severe liver damage by formally withdrawing from the market all prescription combination drug products with more than 325 mg acetaminophen (9). The FDA Center for Drug Evaluation and Research recommendation to limit the dose (10) was an intervention designed to reduce the potential of an overdose occurring if a patient was not using acetaminophen properly or if, unknowingly, a patient was using multiple acetaminophen-containing products (11). In anticipation, McNEIL-PPC, Inc (Fort Washington, PA), the producer of the Tylenol brand of acetaminophen, has already lowered the maximum recommended daily dose for single-ingredient Extra Strength TYLENOL from 4000 mg/d to 3000 mg/d (12, 13). Recent evidence also suggests that acetaminophen has significant adverse effects when taken at recommended doses during pregnancy. If this reflects causality, the safety of acetaminophen during pregnancy must be questioned.

Finally, it is becoming increasingly clear that acetaminophen-induced antinociception is derived from synergism between peripheral, spinal, and supraspinal sites (14, 15). A clearer understanding of these mechanisms holds the key to reducing acetaminophen-related adverse effects while optimizing analgesia. The purpose of this article was to discuss new issues related to safety, labeling, dosing, and a better understanding of the antinociceptive action of acetaminophen.

Pharmacology of Acetaminophen

Mechanisms of Action

For many decades, the mechanism of action of acetaminophen was unclear. It is now known that acetaminophen blocks prostaglandin synthesis from arachidonic acid by inhibiting the enzymes cyclooxygenase (COX)-1 and -2. There are 2 sources of arachidonic acid. In most tissues, cytosolic phospholipase A_2 hydrolyzes phospholipids to yield arachidonic acid. In the brain, liver, and lung, monoacylglycerol lipase hydrolyzes the endocannabinoid 2-arachidonoylglycerol to liberate arachidonic acid (16). Therapeutic concentrations of acetaminophen inhibit COX activity when the levels of arachidonic acid and peroxide are low but have little effect when the levels of arachidonic acid

or peroxide are high as seen in severe inflammatory conditions such as rheumatoid arthritis (17, 18). In addition to its direct effect on COX, acetaminophen also inhibits prostaglandin synthesis by scavenging peroxynitrite, an activator of COX (19).

Like nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen has both central and peripheral effects. Considerable evidence supports a central effect of acetaminophen on prostaglandin synthesis, whereas a smaller number of studies show that it also inhibits prostaglandin synthesis in the peripheral tissues. The first study to show a central effect of acetaminophen was published in 1972 by Flower and Vane (20). Subsequent studies show that acetaminophen inhibits central prostaglandin E2 synthesis after administration of pyrogens or noxious peripheral stimulation (21–23). Acetaminophen also effects prostaglandin synthesis in the peripheral tissues. For example, administration of acetaminophen reduces prostaglandin E2 release in the surgical sites after third molar extraction (24). Unlike NSAIDs, acetaminophen also inhibits myeloperoxidase and may slow the development of diseases such as rheumatic disease and atherosclerosis.

In addition to its effects on COX, the antinociceptive effects of acetaminophen are linked to endogenous neurotransmitter systems including the opioid (25, 26), cannabinoid (27, 28), and serotonergic systems (29, 30). Inhibitors of endogenous opioids, endogenous cannabinoids, and serotonin (5-hydorxytryptamine) attenuate the antinociceptive effect of acetaminophen. The antinociceptive effects of acetaminophen may also be mediated via inhibition of neurotransmitters in the central nervous system. For example, acetaminophen administration attenuates the nociceptive behavior elicited by intrathecal administration of the neurotransmitters glutamate, N-methyl-D-aspartate (NMDA), and substance P (31–33).

Another hypothesis for the analgesic effect of acetaminophen centers on its active metabolite AM404 (27). This is a brain-specific lipoamino acid that inhibits the production of prostaglandins, inhibits allodynia in rats, and targets the ion channel TRPV1 (27, 34). It has recently been shown that AM404 induces analgesia through a supraspinal mechanism, namely TRPV1-dependent $Ca_v3.2$ current inhibition (35). Although these findings are exciting, the AM404 hypothesis continues to be controversial because all current evidence is based on rodent models.

Absorption

The absorption of acetaminophen after oral administration is from the small intestine, and the rate of absorption depends on the rate of gastric emptying. Food in the stomach and concomitant use of certain other drugs such as opioids and anticholinergic agents may delay gastric emptying (36–39). Caffeine accelerates the absorption of acetaminophen (and decreases its clearance), which may account for the increased analgesic effect noted when the 2 are taken together (40). Acetaminophen has excellent bioavailability (≈98%). Onset of analgesia is about 30 minutes, and peak plasma concentrations are reached within 30 to 60 minutes.

Distribution

The plasma protein binding of acetaminophen is low (<25%); consequently, it is readily distributed throughout the body (39). The ratio of concentrations in red blood cells and plasma is ~1.2:1 (41), which affects whole-body pharmacokinetics (42). Acetaminophen crosses both the blood-brain barrier and (43) placental barrier (44, 45). Its plasma half-life is ~1.5 to 2.5 hours (39).

Disposition (Metabolism and Excretion)

Normally, acetaminophen undergoes hepatic conjugation by glucuronosyltransferase (20%–46%) and sulfotransferase (20%–46%) into acetaminophen glucuronide and acetaminophen sulfate, respectively (39, 46). Glucuronidation, sulfation, and subsequent renal excretion normally remove about 85%–90% of a therapeutic dose of acetaminophen. However, after large doses of acetaminophen, these pathways can become saturated.

About 10% of acetaminophen is normally metabolized by CYP450 isoenzymes 2E1 and, to a lesser extent, 1A2, 3A4, and 2A6. A product of this pathway is the highly reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI). After large doses of acetaminophen or when the relevant CYP450 isoenzymes are induced by other drugs or chronic alcohol consumption, NAPQI may accumulate in high concentrations (47–50). Normally, NAPQI is detoxified into harmless metabolites by conjugation of the sulfhydryl groups of glutathione by glutathione S-transferase into mercapturic acid, which is eliminated in the urine (47, 50, 51). However, glutathione can become depleted after large doses of acetaminophen or in cases of malnutrition, allowing NAPQI to accumulate. When this happens, NAPQI interacts covalently with liver cell components, resulting in hepatic damage.

Therapeutic Considerations

The best evidence for the efficacy of analgesics comes from systematic reviews and meta-analysis of randomized double-blind controlled trials (52–57). However, direct head-to-head trials are not always available. An alternative with direct clinical application is to calculate the number needed to treat (NNT) (ie, the number of patients needed to treat with drug A to achieve an improvement in outcome compared with drug B for a treatment period of C) (58). The NNT always specifies the comparator, the therapeutic outcome, and the duration of treatment that is necessary to achieve the outcome. Analgesic efficacy expressed as the NNT relates the number of patients who need to receive the active drug for 1 patient to achieve at least 50% relief of pain compared with placebo over a 4- to 6-hour treatment period (59). Consequently, the NNT allows for the comparison of analgesics in the absence of head-to-head trials.

In view of the decision by the FDA and the pharmaceutical industry to formally withdraw from the market all prescription combination analgesic formulations containing more than 325 mg acetaminophen, it is relevant to review the analgesic efficacy of acetaminophen (2-tablet or 2-capsule doses may still be prescribed, if appropriate) vis-à-vis other available analgesic options. To this end, the Oxford league table of analgesic efficacy (Table 1), predicated on the NNT, is a useful resource. Internal validation of the Oxford league table of analgesic efficacy is provided by indirect comparisons of dose-response relationships. In all cases, higher doses provide better analgesia and lower NNTs (55, 59–63). External validation of the Oxford league table of analgesic efficacy is predicated on a systematic review that compared acetaminophen and NSAIDs in head-to-head trials and found that NSAIDs were consistently better than 1000 mg acetaminophen in dental pain models (64).

Satisfactory relief of odontogenic pain can be attained through an approach that incorporates disease-modifying procedures (ie, primary dental care) and, when indicated, the administration of a disease-modifying analgesic. Disease-modifying analgesics not only modulate chemical activator–induced nociception, but they also have anti-inflammatory properties affecting vascular tone and permeability, leukocyte recruitment, and the synthesis of cytokines. Based on the NNT, acetaminophen is the least effective analgesic available for the management of odontogenic pain. However, it is of note that a full dose of