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Confusion

Acetaminophen Dosing Changes Based on NO Evidence in Adults

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Abstract

Acetaminophen (paracetamol) plays a vital role in American health care, with in excess of 25 billion doses being used annually as a nonprescription medication. Over 200 million acetaminophen-containing prescriptions, usually in combination with an opioid, are dispensed annually. While acetaminophen is recognized as a safe and effective analgesic and antipyretic, it is also associated with significant morbidity and mortality (hepatotoxicity) if doses in excess of the therapeutic amount are ingested inappropriately. The maximum daily therapeutic dose of 3900–4000 mg was established in separate actions in 1977 and 1988, respectively, via the Food and Drug Administration (FDA) monograph process for nonprescription medications. The FDA has conducted multiple advisory committee meetings to evaluate acetaminophen and its safety profile, and has suggested (but not mandated) a reduction in the maximum daily dosage from 3900–4000 mg to 3000–3250 mg. In 2011, McNeil, the producer of the Tylenol® brand of acetaminophen, voluntarily reduced the maximum daily dose of its 500 mg tablet product to 3000 mg/day, and it has pledged to change the labeling of its 325 mg/tablet product to reflect a maximum of 3250 mg/day. Generic manufacturers have not changed their dosing regimens and they have remained consistent with the established monograph dose. Therefore, confusion will be inevitable as both consumers and health care professionals try to determine the proper therapeutic dose of acetaminophen. Which is the correct dose of acetaminophen: 3000 mg if 500 mg tablets are used, 3250 mg with 325 mg tablets, or 3900 mg when 650 mg arthritis-strength products are used?

In 1960, acetaminophen (paracetamol) was introduced in the United States as a nonprescription analgesic and antipyretic.[1] It now plays a vital role in American health care, with in excess of 25 billion doses being used annually as a nonprescription medication.[2] Additionally, over 200 million acetaminophen-containing prescriptions, usually in combination with an opioid, are dispensed annually.[2] Most nonprescription acetaminophen-containing products are regulated by the Food and Drug Administration (FDA) drug monograph process.

Under the monograph regulatory process, once a pharmaceutical is recognized as being safe and effective for the general public to use without the need to seek treatment by a health care professional, a monograph is established. To market the product, a manufacturer merely needs to

comply with the conditions of the monograph, which include parameters such as indications and dosage; no additional pre-market approval is necessary. Acetaminophen is a classic example of a pharmaceutical that is subject to the nonprescription drug monograph process as found in the 'Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use' monograph.[3] The monograph specifies that single-ingredient acetaminophen-containing products that contain 325 mg should be administered in a dose of 325–650 mg every 4 hours while symptoms persist, not to exceed 3900 mg in 24 hours for not more than 10 days (approved July 8, 1977). Products that contain 500 mg should follow the dosing regimen of adult doses up to 1000 mg, not to exceed 4000 mg in 24 hours (approved November 16, 1988). The 650 mg sustained-release products are governed not by the monograph process but instead by the FDA New Drug Application (NDA) process.[1] All prescription products that contain acetaminophen must receive FDA approval via the NDA process and, unlike the monograph process, no dosing modifications may occur without prior FDA approval.

While the monograph process dictates acetaminophen dosing, acetaminophen has come under significant FDA scrutiny, and the FDA has become increasingly vigilant with regard to the use of this medication, because of the occurrence of hepatotoxicity when acetaminophen is not used properly. Hepatotoxicity has been recognized as being associated with inappropriate use of acetaminophen for over six decades.[4] Acetaminophen has been cited as the leading cause of drug-induced acute liver failure in the United States.[5-7] An estimated 78 414 emergency department visits for the treatment of acetaminophen overdose occur annually.[8] Over the last two decades, the FDA has held four advisory committee meetings to address the toxicity-related issues associated with acetaminophen. The most recent advisory committee meeting, which dealt with the issue of adult acetaminophen overdose, was conducted in 2009 and formed the basis for current decisions that are being made by the FDA and industry about how to dose acetaminophen in both nonprescription and prescription products.[9]

To address the issues surrounding acetaminophen toxicity, the FDA Center for Drug Evaluation and Research (CDER) prepared an internal report that formed the basis for discussion at the 2009 advisory committee meeting. The committee members were asked to vote upon several recommendations, which included reducing the total daily acetaminophen dose from 4000 mg to 3250 mg, limiting tablet strength to 325 mg/tablet, and switching the 500 mg strength to prescription status.[9] The advisory committee was generally sympathetic to these interventions as ways to reduce acetaminophen toxicity.[9] As with all advisory committees, the committee was purely 'advisory' to the FDA, and its recommendations were not binding to the FDA. However, the recommendations of the CDER group and the advisory committee and subsequent actions by the FDA and voluntary actions by industry have created significant confusion about the therapeutic or 'proper' dose of acetaminophen.

What is the maximum safe daily dose of acetaminophen? In reality, the FDA has never validated the threshold toxic dose for the average adult. The 3900 mg maximum daily dose, as recommended originally, was deemed to be safe and is five to seven times lower than the estimated median lethal dose (LD_{50}) of 400 mg/kg. The 1977 panel used anecdotal reports suggesting that 15 g was the hepatotoxic dose; therefore, a dose of 650 mg was 23 times less than the hepatotoxic dose. Subsequently, the analgesic monograph dictated that 3900–4000 mg was a safe and effective maximum daily dose if acetaminophen was used properly and according to the approved labeling. History has demonstrated the safety of this dose.

In 1994, Whitcomb and Block published the results of their retrospective case series review of 126 779 hospital discharge summaries from the University of Pittsburgh Medical Center to identify those patients who were taking acetaminophen and who developed severe hepatotoxicity.[10] Forty-nine patients with severe acetaminophen-induced hepatotoxicity (defined as an aspartate aminotransaminase level >1000 U/L) were identified: 28 patients had an intentional acetaminophen overdose, and 21 were taking acetaminophen for therapeutic reasons. All of these patients had taken

more than the recommended daily maximum dose of 4000 mg. No hepatotoxicity was identified in patients who had therapeutic doses of acetaminophen or less than 4000 mg/day. A prospective study by den Hertog and colleagues evaluated the use of acetaminophen in 697 stroke patients who received a dose of 6000 mg daily for 3 days. None of the patients had liver enzyme changes.[11] Temple and colleagues studied osteoarthritis in patients who received acetaminophen 4000 mg daily for 6–12 months, and none of the patients experienced liver function tests that exceeded two times the upper limit of the normal range.[12] These studies and a multitude of others support the fact that 4000 mg is a safe maximum daily dose.

The FDA CDER recommendation to reduce the maximum daily dose to 3250 mg was therefore not evidence based but merely a hypothetical intervention 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. In other words, the expressed concern was not with therapeutic dosing (≤4000 mg/24 hours) but with excessive dosing when two or more products containing acetaminophen are taken inadvertently, and the potential for hepatotoxicity with chronic use at excessive doses.

Consequently, a unilateral decision on July 28, 2011, was made by McNeil, the manufacturer of the Tylenol® brand of acetaminophen, to modify the current label and dosage regimen (which is permitted under the monograph process) of its 500 mg/tablet product, for patients who are not under the care of a health care professional, to six doses (3000 mg) daily. This decision was not mandated by the FDA, and generic acetaminophen manufacturers did not follow suit. Ironically, the recommended doses of the Tylenol® brand 325 mg tablets and 650 mg sustained-release products remain the same. For both products, McNeil's recommendations continue to allow a maximum daily dose of 3900 mg. While McNeil has announced plans to modify the doses of the 325 mg strength in 2012, it is not obligated to do so, and its unilateral action does not obligate any other manufacturers to modify their dosing regimens, as is consistent with the monograph process. However, this decision has the potential to be misinterpreted by many as an FDA mandate that was implemented for safety reasons.

Confusion in the metric-system–challenged American society is likely to occur. Even among health care professionals, acetaminophen-dosing–related confusion is a distinct possibility. For example, if hospitals change their dosage guidelines and apply the new McNeil-initiated 500 mg recommendations (a maximum of 3000 mg daily) designed for outpatients not under health care practitioner supervision to all acetaminophen products (inappropriately) in the controlled hospital environment, there may be negative patient care ramifications. Conceivably, a physician could prescribe inadequate dose regimens of the intravenous form of acetaminophen, assuming incorrectly that the McNeil announcement applies to all routes of acetaminophen administration instead of the FDA monograph-approved 1000 mg single dose and 4000 mg daily maximum, and thereby compromise analgesic or antipyretic therapy.[13] Given the pharmacokinetics of acetaminophen (an elimination half-life of 2–3 hours), lengthening the dosing interval (e.g. 1000 mg every 8 hours to stay within the maximum daily dose as recommended in the McNeil guideline) may cause individuals with pain or fever to be subject to therapeutic failure in the latter part of their dosing regimen. Another potential source of confusion exists if a health care provider, such as a pharmacist, nurse or physician, understands that the McNeil changes are voluntary and recommends the traditional monograph-approved dosing regimen of up to 4000 mg daily, thus creating confusion among uninformed health care providers and the general public as to what is a therapeutic and safe dose of acetaminophen.

To paraphrase Paracelsus, "the dose differentiates a remedy from a poison" and the 4000 mg dose has been established as both safe and effective. Does the new lower dosing, as recommended by the industry leader, suggest that doses in excess of 3000 mg are no longer safe? If more than 3000 mg is administered in a 24-hour period, will a hospital be obliged to complete a medication safety error report? Will consumers contact poi-

son centers or their health care providers when they determine that they have exceeded the 'new' 3000 mg maximum daily dose, leading to even more confusion when they are informed that only daily doses that exceed 4000 mg in adults are considered excessive? Complicating the dilemma will be the inevitability that patients will receive conflicting advice when they speak to multiple caregivers.

The voluntary decision to reduce the maximum daily dose of acetaminophen may exert undue pressure on the generic acetaminophen manufacturers to adjust their dosing recommendations accordingly, despite the fact that there is no evidence basis for changing the traditional dosing regimen. Ultimately, this may result in inadequate pain relief and confusion, and may not produce the anticipated reduction in the number of acetaminophen-related emergency department visits and the associated morbidity and mortality. The fact remains that nearly 70% of acetaminophen-related emergency department visits result from self-directed violence such as suicide attempts;[7] a change in dosing strategies is unlikely to have an impact on self-harm incidents. Furthermore, considering the astronomical figure that over 25 billion doses of acetaminophen are used annually by the American public, the toxicity signal related to acetaminophen is extraordinarily low and is further evidence that the traditional dosing regimen of acetaminophen is safe. Which is the correct dose of acetaminophen: 3000 mg if 500 mg tablets are used, 3250 mg with 325 mg tablets, or 3900 mg when 650 mg arthritis-strength products are used? The pessimistic viewpoint is that the likely consequence of changing from the traditional daily maximum acetaminophen dose of 4000 mg will be an onslaught of confused patients and fellow health care professionals!

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