

New Perspectives on Acetaminophen and Alcohol Use

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Acetaminophen is one of the most commonly used over-the-counter (OTC) analgesics and antipyretics. For more than 50 years in the United States, acetaminophen, when used appropriately at therapeutic doses, has been shown to be extremely safe in virtually all patient populations. Despite this remarkable time-tested safety profile, in recent years, some healthcare providers have questioned the safety of acetaminophen use by alcoholic patients and patients who drink alcohol.¹ These initial, presumably well-intentioned yet scientifically unproven concerns spread rapidly in both the medical literature and the lay press. This unsubstantiated concern that therapeutic doses of acetaminophen, less than or equal to 4 g/day, may cause life-threatening hepatotoxicity and fulminant hepatic failure led to an unfounded belief that alcoholic patients and patients who drink alcohol should avoid acetaminophen.

Concerns regarding acetaminophen and alcohol and their effects on the liver are based upon pharmacologic and clinical truths. However, these are the facts: Acute acetaminophen overdose can cause hepatotoxicity and fulminant hepatic failure and chronic alcohol use can cause cirrhosis. The hepatic cytochrome oxidase system, specifically cytochrome P4502E1 (or CYP2E1), is a minor metabolic pathway involved in the metabolism of acetaminophen and alcohol.² Chronic alcohol use can induce the activity of cytochrome P4502E1. Acetaminophen, which is metabolized by cytochrome P4502E1, is converted to a toxic intermediate, N-acetyl-p-benzoquinone imine (NAPQI). Following a therapeutic dose of acetaminophen, the small amount of NAPQI formed is

easily detoxified by glutathione in the liver and does not result in hepatotoxicity. Following an acute acetaminophen overdose, if the amount of NAPQI formed overwhelms the liver's detoxification system, hepatotoxicity and fulminant hepatic failure can result.

Considering these facts it is easy to understand why there would be concern about a possible acetaminophen-alcohol drug-drug interaction. Theory suggests that patients who chronically drink alcohol and have increased their cytochrome P4502E1 activity may be able to generate enough NAPQI from a therapeutic dose of acetaminophen to overwhelm the liver's detoxification mechanism. The fact is that pharmacokinetic and clinical studies in humans have produced conflicting data, the preponderance of which does not support this theoretical concern.³⁻⁷

A small number of case reports and retrospective case series fueled the unfounded belief that alcoholic patients and patients who drink alcohol should avoid acetaminophen. Given the prevalence of acetaminophen and alcohol use and the 5% to 10% rate of alcoholism in the United States, one would expect the medical literature to be replete with evidence supporting this theory.⁸ This is not the case. A recent systematic review of the English literature between 1966 and 1999 identified only 20 reports involving 25 patients containing enough information to even consider the possibility that an alcoholic patient who ingested less than or equal to 4 g/day of acetaminophen would develop hepatotoxicity.⁹ Common weaknesses of these case reports included retrospective data collection that was often incomplete, suspected inaccuracies in the alcoholic patient's history with respect to the dose of acetaminophen

ingested, acetaminophen levels that were more consistent with acute overdose than therapeutic dosing, and failure to exclude other common causes of hepatotoxicity and fulminant hepatic failure. In fact, after critical review only 5 of 25 reports contained enough information to credibly implicate a therapeutic dose of acetaminophen as a cause for the development of hepatotoxicity.

Based upon the small number of credible case reports and the patterns of use and availability of acetaminophen and alcohol, it is reasonable to assume that if an acetaminophen-alcohol drug-drug interaction does exist, that it must be exceedingly rare and probably idiosyncratic. Few healthcare providers who assert that alcoholic patients and patients who drink alcohol should avoid acetaminophen have considered the overall risk or the consequences of this recommendation. If these patients are to be advised to avoid acetaminophen the ramifications of this advice must be considered. It seems likely that patients will use alternative OTC analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs). Because therapeutic doses of NSAIDs can cause gastric ulcers, gastrointestinal bleeding, and increase the risk of death, their use in alcoholic patients can be dangerous.^{10,11} Based upon the available data it is likely that many more alcoholic patients and patients who drink alcohol suffer morbidity and mortality from NSAIDs than from acetaminophen. This is likely an important reason why the US Food and Drug Administration requires that NSAIDs, in addition to acetaminophen, display an alcohol warning on their packages.

Based upon theoretical pharmacologic concerns and a limited number of case reports, the recommendation that alco-

holic patients and patients who drink alcohol should avoid acetaminophen appears to be unsubstantiated. Based upon the current standards of evidence-based medicine, a double-blind, randomized, placebo-controlled study was needed to investigate the effect of maximal daily doses of acetaminophen on the liver of alcoholic patients.

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